REMARKS

Reconsideration of this application is respectfully requested.

Claims 283-438 were previously pending in this application. Claims 283-294, 300, 310, 313, 319, 322, 343-346, 356, 359, 364-375, 379, 382-393, 397, 400-402, 406-408 and 412 have been amended. New claims 439-460 have been added and claims 363, 381, 399 and 405 have been cancelled. Accordingly, claims 283-362, 364-380, 382-398, 400-404 and 406-460 are presented for further examination on the merits.

Applicants and their undersigned attorney acknowledge that the art unit designated to handle this application has been changed. Henceforth, all future correspondence will be directed to Art Unit 1809.

Because of the great number of exhibits attached to this Amendment (48 in all!), Applicants have taken the liberty of also attaching a list that immediately precedes the first exhibit (Exhibit 1).

Even before discussing the amendments to the claims above, Applicants wish to bring to the Examiner's attention that the U.S. Patent Office has already issued three separate patents to three different entities with claims embraced by Applicants' present generic and dominant invention. The first applications for these three issued patents were filed much later than Applicants' May 5, 1983 priority filing date - and in fact, in two instances, applications were filed more than a year and a half later - in December 1985. These three U.S. patents include:

Exhibit	U.S. Pat. Number.	Issue Date	Inventor(s)	Assignee	Priority Filing Date
1	4,716,106	12/29/87	Chiswell	Amersham	3/1/84 (UK) 2/28/85 (US)
2	4,868,105	9/19/89	Urdea et al.	Chiron	12/11/85
3	4,882,269	11/21/89	Schneider et al.	Princeton	12/13/85

In the case of Amersham's U.S. Patent No. 4,716,106 (Exhibit 1), the first issued claim reads:

> 1. A method of detecting a target polynucleotide sequence in a sample, comprising the use of
> (a) a labelled polynucleotide secondary probe having a complex single-stranded polynucleotide sequence, and
> (b) a polynucleotide primary probe having a single-stranded sequence complementary to the target sequence and a complex single-stranded sequence complementary to the complex sequence of the secondary probe,
> which method comprises the steps of
> (i) contacting the sample under hybridisation conditions with the primary probe,
> (ii) before, during or after said contact hybridising the labelled secondary probe to the primary probe, and
> (iii) observing the presence or absence of the label in association with the sample as indicating the presence or absence of the target sequence.

In Chiron's U.S. Patent No. 4,868,105 (Exhibit 2), the first claim recites in part:

> 1. An assay method for detecting a nucleic acid analyte in a sample, employing two sets of reagents, a labelling set and a capturing set, said method comprising:
> (1) providing members of said labelling set of reagents, comprising:
> (a) a plurality of labelling nucleic acid probes comprising single-stranded polynucleotide chains each having two nucleic acid regions, the first region having a nucleic acid sequence L-1 about 15 to about 100 nucleotides in length which is complementary to a sequence of said analyte, and the second, noncomplementary region at most about 5 kb in length and including a labelling reagent recognition sequence L-2, wherein each of said sequences L-1 is complementary to physically distinct, overlapping sequences of said analyte;
> (b) a labelling reagent having a nucleic acid sequence complementary to said labelling reagent recognition sequence L-2 and a label which provides, directly or indirectly, a detectable signal; . . .

And in Princeton's U.S. Patent No. 4,882,269 (Exhibit 3), method and kit claims were issued, an exemplary kit claim reading as follows:

> 25. A hybridization assay kit for the detection of a target nucleotide sequence, comprising:
> (a) a primary probe which comprises a polynucleotide sequence that is complementary to the target nucleotide sequence and a polymeric tail that has binding sites that are incapable of binding to the target sequence; and
> (b) a plurality of secondary probes comprising a family of signal-generating probes each member of which comprises a signal-generating component and a polymer capable of binding to a different

> portion of the tail of the primary probe, which provides for the generation of an amplified signal when the polynucleotide sequence of the primary probe is hybridized to the target nucleotide and the plurality of secondary probes are bound to different portions of the primary probe tail.

As indicated by the issuance of three above-described U.S. patents (Exhibits 1-3), the U.S. Patent Office has already in effect deemed Applicants' universal detection system to be new, unobvious and patentable. This is compelling evidence on the patentability of the present invention, and should fully and thoroughly considered, together with developments in other significant patent examining authorities, discussed *infra* (see this Amendment, page 37, first paragraph, through page 39, first paragraph). Even more significant are the characterizations by other applicants and their attorneys of the same prior art cited against the instant claims - and the acceptance of those characterizations by the U.S. Patent Office and the examiners handling those other applications who allowed and issued patents. This point too, is discussed *infra*, in connection with the Dunn et al. (1977) article cited in the prior art rejections under Sections 102 and 103(a). As set forth below, one could never practice the present invention except by grossly modifying Dunn's disclosure to the point of destroying the intent, purpose or function of Dunn's sandwich hybridization technique. See this Amendment, page 78 through page 79, penultimate paragraph.

Turning to the amendments in this paper, Applicants have amended several claims above in a sincere effort to define their invention more clearly and/or to meet the Examiner's requirements or to adopt his suggestions. In three instances, very minor punctuation or grammatical corrections have been made (claims 319, 322 and 412). Other more significant amendments to the claims have been made as described further below.

First, commensurate with Applicants' complete and broad disclosure, all of the claims have been amended with respect to the signalling entity. Thus, all of the independent composition claims (283-294) and newly-added independent process claims (443-460) now recite "one or more signalling entities substantially incapable of binding to or hybridizing with the molecularly recognizable portion on said analyte." By adding that clear and precise limitation to the claims, Applicants have plainly eschewed any notion or resemblance to the classical sandwich hybridization technique in their invention. Sandwich hybridization in which the analyte "meat" of the sandwich is flanked by two adjacent, non-overlapping probes was disclosed by

Dunn et al. and Ranki et al., both cited of record in this application. Support for the foregoing phrase is found throughout the disclosure, including the originally filed claims that were directed to "a [single] signalling entity." The reference to multiple signalling entities ("or more") is found in two signficant passages in the disclosure, page 16, first paragraph; and page 22, first paragraph.

Language that the signalling entities are "substantially incapable of binding to or hybridizing with the molecular recognizable portion is also well suppoted in the specification. In the specification on page 14, full paragraph, it is disclosed:

> The second portion of the molecular bridging entity must comprise a polynucleotide sequence. The polynucleotide sequence can be any chosen sequence, provided that it is long enough to provide stable annealing with a complementary sequence under given stringency conditions, that it be complementary to the polynucleotide sequence on the signalling entity, and, if the recognizing portion on the bridging entity is itself a polynucleotide sequence, that it be sufficiently different from said recognizing sequence portion, to avoid hybrid formation between the analyte sequence and the second polynucleotide portion on the bridging entity. The latter of the three conditions is required to prevent molecular confusion with concommitant appearance of false results.

From the foregoing description, it is clear that the second portion of the molecular bridging entity must comprise a polynucleotide sequence that is sufficiently different from the analyte to avoid hybrid formation between the analyte sequence (or molecularly recognizable portion). Because the signalling entity nucleic acid portion is complementary to the molecular bridging entity nucleic acid second portion, it is self-evident from the very disclosure itself that the former must *ipso facto* be different from the analyte to avoid hybrid formation between the signalling entity nucleic acid portion and the analyte, that would otherwise create a false (positive) result.

Second, the phrase "more than one" has been inserted in front of the "bridging entity nucleic acid second portion" in each of claims 287-290. By so doing, a proper antecedent basis has been restored in these claims. **Third**, the second element in the second part of the composition recited in each of claims 291-294 has been amended to recite "one or more chemically modified or artificially altered polynucleotides capable of providing a detectable signal." As the Examiner astutely observed in the Office Action, claims 291-294 lacked any designation of what performs the signalling function in the claim. The foregoing amendment to claims 291-294 makes it clear that it is the chemically modified or

artificially altered polynucleotides that perform the signalling function in the composition. **Fourth**, clarification has been made to the "nucleic acid" recited in dependent claims 300 and 310. In the case of the former claim, the language now reads "said analyte nucleic acid;" and in the latter claim, the language now reads "said molecular bridging recognizing first portion nucleic acid." A similar amendment was made to claim 313 above where the single-stranded or partially double-stranded oligo- or polynucleotide has been identified as being in the molecular bridging entity recognizing first portion.

Fifth, the word "entity" in claim 356 has been changed to "entities" so as to conform the "molecular bridging entities" with the plural form recited in the twelve independent claims from which claim 356 depends. **Sixth**, dependent process claims 364, 365, 382 and 383 have each been amended by adding the phrase "recited in said forming step" at the end of each claim. In this way, it is made clear to the reader that the complex formed "thereafter" is the same complex recited in said forming step.

Seventh, four detection process claims, 363, 381, 399 and 405, previously dependent on several of the composition claims, have now been canceled and recast as eighteen separate independent claims. Commensurate with Applicants' broad and complete disclosure, the new process claims, 444-460, are directed to the use of a composition in which one or more signalling entities are recited. As it is well known and accepted in the art (even by the authors themselves years after their 1977 Cell paper cited against the instant pending claims), Dunn and Hassell never performed or even contemplated any detection of an unknown analyte. Applicants' presently claimed detection process reciting one or more signalling entities (and one or more molecular bridging entities) is clearly novel and unobvious over the prior art, including Dunn and Hassell who were only concerned with RNA transcript mapping involving known analytes. As elaborated in much greater detail below, Applicants' claimed invention is patentably distinguished from Dunn and Hassell who disclosed an altogether different composition and an altogether different process from the universal system set forth in the instant claims. See discussion *infra* (this Amendment, page 61, last paragraph, through page 70, first full paragraph). Other than the substitution of "one or more signalling entities" for "more than one signalling entities," the new independent process claims, 444-460, conform to the subject matter in the corresponding composition claims. Thus, no further search or examination should be necessitated by the replacement of the four canceled process claims with the new independent claims. As a consequence of

the cancellation of claims 363, 381, 399 and 405, and the addition of new independent claims 444-460, it was necessary to change the dependencies in other dependent claims so that they would not be dependent on otherwise canceled base claims. The dependent process claims so affected included claims 364-366, 370, 374-375, 379, 382-384, 388, 392-393, 397, 400-402 and 406-408.

Eighth, direct detection as a process step has been clarified in claims 366-369, 371-373 and 385-387. The Examiner had noted in the Office Action that the phrase "wherein said detecting step the direct" detectable signal in these claims was awkwardly worded. Reference in the foregoing claims as amended is to a "directly detectable signal" or an "indirectly detectable signal" as the case may be. For example, claim 366 recites "wherein detecting is carried out by means of a directly detectable signal provided by said signal generating portion." Claims 367 and 368 depend from claim 366, and each now recites "wherein said detecting step the directly detectable signal providing signal generating portion."

Ninth, claims 365, 383, 401 and 407 have been amended in response to the new matter issue raised in connection with the objection and rejection under 35 U.S.C. §112, first paragraph. Each of these claims are dependent process embodiments wherein complex formation involves contacting the bridging entity with the signalling entity to form a first complex which is contacted with the analyte to form a further complex recited in the forming step. As now amended, these claims recite that "said forming step comprises contacting said bridging entity with said signalling entity under conditions sufficient to form a first complex and thereafter contacting the first complex with said analyte under conditions sufficient to form said complex . . . recited in said forming step." The added phrases "under conditions sufficient" are taken from the specification, page 28, second paragraph. There, Applicants disclose: "Hybridization of the bridging entity strand to the signalling entity strand is carried out under hybridizing conditions and under any set of stringency conditions." Previously in that same paragraph, Applicants disclose: The composition suspected of containing the analyte is incubated with the bridging entity for a time and under conditions sufficient to allow complexation . . ." It is believed that the disclosure in that paragraph fully supports the language in claims 365, 383, 401 and 407 that complex formation occurs as a result of contacting the variously recited elements under conditions sufficient to form such complexes. Claims 404 and 410 are also affected by the foregoing amendments by virtue of their dependencies.

Tenth, the phrase "a binding step on an insoluble phase" has been deleted as a Markush member from claims 374 and 392. The Examiner had drawn attention to the fact that originally filed claim 65 indicated that the detecting step *per se* is only limited to comprise a binding step on an insoluble phase. In order to meet the Examiner's requirement in this instance, new claims 440 and 441 have been added, both of which recite "wherein said step of detecting the analyte by a signal provided by said signal generating portion or portions present in said complex comprises a binding step on an insoluble phase." New claims 439 and 440 conform to the language in original claim 65.

Eleventh, the indirect detection language has been clarified with respect to claims 343-346, 370-373 and 388-391. These are claims somewhat counterpoint to claims 366-369, 371-373 and 385-387, discussed above in the preceding sixth point, *infra*. In claim 343, for example, the amended language reads "wherein said signal generating portion or said one or more chemically modified or artificially altered polynucleotides are capable of providing an indirectly detectable signal. Three claims, 344, 345 and 346, depend from claim 343, and each now recites "wherein said indirectly detectable signal providing signal generating portion" . . .

Finally, new claims 441 and 442 have been added commensurate with Applicants' complete and broad disclosure. Claim 441 is directed to the composition according to claim 309, wherein the nucleic acid in said molecular bridging entity recognizing first portion and said molecular bridging entity nucleic acid second portion are incapable of hybridizing to identical oligo- or polynucleotide sequences. Support for new claim 441 is found in the specification, page 14, full paragraph. Earlier versions of claim 441 can be found in related predecessor applications in the family. See, for example, claim 186 presented in Applicants' August 10, 1993 Second Preliminary Amendment that was submitted in U.S. Patent Application Serial No. 08/032,769, filed on March 16, 1993. Prior claim 186 read:

> The method of claim 173, wherein said molecular bridging entity first portion and said molecular bridging entity second portion are incapable of hybridizing to identical oligo- or polynucleotide sequences.

A process claim with a similar limitation has also been added as new claim 442. The latter is directed to a detection process in which the composition of new claim 441 is provided and used to detect an analyte. As in the case of claim 441,

support for claim 442 is found on page 14 (full paragraph) in the specification.

It is believed that all of the foregoing amendments to the claims and the newly added claim are fully supported by the original specification, and thus, none constitutes the insertion of new matter in the disclosure. By and large, a great many of the amendments have been made either in direct response to the Examiner's remarks or to adopt the Examiner's suggestions or position on a particular point. Entry of all of the amendments is respectfully urged.

Before addressing the substantive issues raised in the March 10, 1997 Office Action, Applicants and their attorney would like to take care of some administrative matters, as well as to apprise the Examiner of developments in other countries involving related applications or patents in the family.

Information Disclosure Statement & Previously Submitted PTO Forms 1449 & 892

On the next to the last page of the Office Action, the Examiner indicated that the PTO Forms 1449 and 892 in the prior parent applications are not in the present application because it was filed as a continuation application under 37 C.F.R. §1.60. In response to the Examiner's request for such forms, Applicants and their undersigned attorney have made an exhaustive search through all the prior patent applications and foreign files for any art-related documents, including the requested PTO Forms 1449 and 892. Concurrently with this Amendment, Applicants are filing an Information Disclosure Statement in which copies of the executed PTO Forms 1449 and 892 from prior parent applications (total of 25 sheets) are being submitted for inclusion and reference in this application. In addition to the executed forms, Applicants are also submitting copies of 36 documents which fall into one of the following two categories:

documents considered by other examiners but not the present Examiner (total of 30 documents);

or

documents not considered by any examiner (total of 6 documents).

Other information has been included in the accompanying IDS to assist the Examiner in tracking the origin of the submitted documents or to follow the actions

of other previous examiners. Applicants are confident that the universe of art-related documents (total of 72 documents ever cited in the instant application or predecessor applications) is embraced by the accompanying IDS. Applicants do not expect that further art material to the examination of this application will come to light. Still, it is possible since neither the current European opposition nor the opposition period for their corresponding Japanese patent, both discussed in the next section, has not been concluded or passed. Nevertheless, if any other art does come to their attention, Applicants and their attorney will submit them forthright to the Examiner for consideration in this application.

Developments in Other Patent Examining Authorities

It is extremely noteworthy that three other significant patent examining authorities have determined that Applicants' invention is novel, unobvious and wholly deserving of broad patent protection. In this regard, Applicants wish to bring to the Examiner's attention that patents have been issued or applications have been recently allowed by the Canadian Intellectual Property Office (CIPO), the Japanese Patent Office (JPO) and the European Patent Office (EPO) - all based upon the priority document, U.S. Patent Application Serial No. 06/491,929, filed on May 5, 1983.

Canadian Intellectual Property Office (CIPO)

The CIPO issued Canadian Patent No. 1,228,811 on November 3, 1987. This patent is directed to method and kits. A copy of Canadian Patent No. 1,228,811 is attached as Exhibit 4. A pending divisional application for composition claims is awaiting a first office action.

Japanese Patent Office (JPO)

The Japanese Patent Office issued on November 7, 1996 Japanese Patent No. 2577881 that covers a wide range of subject matter. Japanese Patent No. 2577881 was published on February 5, 1997 and its 149 claims cover methods for detection (claims 1-84), kits (85-134) and compositions (135-149). A copy of the Japanese Letters Patent, the published Japanese patent document and the issued

claims (1-149) are attached as Exhibit 5. It is the understanding of Applicants' attorney that the Japanese examiner was so impressed with the invention that no restriction requirement in the form of a unity of invention rejection was imposed with respect to the number of independent claims and numerous embodiments claimed in the application. As indicated above, the Japanese patent is in the opposition period. To date, no indication of any opposition lodged against the patent has been received from Applicants' Japanese associates. Applicants will apprise the Examiner of any developments that take place in Japan with respect to their corresponding Japanese patent.

European Patent Office (EPO)

The EPO granted European Patent No. 0 128 332 B1 on August 2, 1995 for detection methods, polynucleotide compositions and kit. A copy of EP 0 128 332 B1 is attached as Exhibit 6. A divisional application directed to other compositions of the present invention was filed and is still pending in the EPO. An opposition was lodged against this patent last year by Tm Technologies, Inc. citing the following documents in support of its argument of invalidity:

1. Dunn and Hassell, Cell 12:23-26 (1977);
2. Dunn and Sambrook, Methods in Enzymology, 65:468-478 (1980);
3. Ranki et al., Curr. Top. Microbiol. Immunol. 104:307-318 (1983);
4. Ranki et al., Gene 21:77-85 (1983);
5. European Patent Application Publication No. 0 079 139 A;
6. PCT/FI 82/00038; and
7. European Patent Application Publication No. 0 124 221 A1.

The Applicant responded to the Opponent Tm Technologies' arguments on March 3, 1997. To date, no reply has been received by Applicant's European associates handling the opposition.

Of the seven above-listed documents, the first, second, sixth and last listed were considered in the instant application or related predecessor applications. As discussed *supra*, copies of the other three documents (nos. 3-6) that were not considered by the Examiner are being submitted herewith in a concurrently filed Information Disclosure Statement that includes a completed form PTO-1449. Consideration of the three documents submitted in the accompanying IDS is

respectfully requested.

With respect to the last-listed document, EP 0 124 221 A1, this document was cited as a basis for rejection in a predecessor application, Serial No. 07/607,787. That rejections was withdrawn, however, when it was pointed out to the examiner that EP 0 124 221 A1 bore a publication date after Applicants' May 5, 1983 priority filing date. In any case, it seems clear that whatever invention was disclosed in EP 0 124 221 A1 has long since been abandoned by the proprietor and inventors because the European prosecution has long since ceased to the point that the European Patent Office has destroyed the file wrapper. This means that no copies of the file wrappers are available to the public. And neither has prosecution been undertaken elsewhere in the world according to a recent computer search for this patent document.

Applicants respectfully request that consideration be given to these other developments in other patent offices throughout the world as described above and supported in the attached exhibits referenced hereinabove. It is obviously no coincidence that a literal stream of patent examiners have seen fit to issue several patents with broad claim coverage for Applicants' invention.

The Objection and Rejection Under 35 U.S.C. §112, First Paragraph

The specification stands objected to and claims 300, 313, 315, 317-319, 321, 328, 331, 365, 383, 401, 404, 407 and 410 were rejected under U.S.C. §112, first paragraph, for not providing support for the invention as is now claimed. In the Office Action (pages 2-3), the Examiner stated:

> [1] In claim 300, lines 3-4, the phrase "analog-containing polymer" which adds NEW MATTER in that written basis for generic polymers containing analogs has not been found. Consideration of the support cited by applicants reveals that polynucleotides of various types are listed but not more generic polymers. Another interpretation is that NEW MATTER is added via unclarity of the metes and bounds of such polymers. Claims 315, 321, and 328 also contain this new matter and claims 317 and 318 via dependence from the above claims.
>
> [2] In claim 313, line 2, the phrase "partially double-stranded" is given. Consideration of the written support as filed has failed to reveal any written basis for "partially" doubled-stranded. This "partially" is therefore NEW MATTER. Claims 319 and 331 also contain this NEW MATTER.

> [3] Claims 365, 383, 401, and 407 are directed to a specific order of complex formation wherein the bridging entity is first contacted with the signalling entity to form a first complex followed by contacting this first complex with the analyte. Consideration of the support cited by applicants on pages 33-34 has not revealed a written basis for this order of complex formation. Therefore the limitations in claims 365, 383, 401, and 407 directed to the above summarized order lack written basis as filed and contain NEW MATTER and claims 404 and 410 via dependence from the above claims.

The objection and rejection for new matter are respectfully traversed.

The remarks that follow are directed to each of the four matters bracketed above.

[1] Regarding the phrase "analog-containing polymer," Applicants respectfully disagree that this phrase adds new matter to the disclosure. In fact, the specification is replete with descriptions for generic polymers including polynucleotides, proteins and polysaccharides. A thorough discussion of polynucleotides is found in several portions in the specification, including page 14, first full paragraph, through page 15, first paragraph; and page 16, second paragraph, through page 18, first paragraph. Proteins and polysaccharides are liberally mentioned throughout the specification. See, for example, page 11, second paragraph, through page 14, first paragraph. Beginning with the second paragraph on page 11, and continuing through page 12, first paragraph, reference is specifically made to:

> proteins, polysaccharides, lipopolysaccharides, protein complexes . . . Among the most common proteins are the structural proteins, enzymes, immunoglobulins or fragments thereof.

Later on page 12, second paragraph, continuing through page 14, first paragraph, it is disclosed:

> A molecularly recognizable portion on an analyte may be, for example, . . . an antigen portion, to be recognized by its corresponding monoclonal or polyclonal antibody; an antibody portion, to be recognized by its corresponding antigen, a lectin portion, to be recognized by its sugar; a sugar portion, to be recognized by its lectin; a hormone portion, to be recognized by its receptor; a receptor portion, to be recognized by its hormone; an inhibitor portion, to be recognized by its enzyme; an enzyme portion, to be recognized by its inhibitor; a cofactor portion, to be recognized by a cofactor enzyme binding site; a cofactor enzyme binding site portion, to be recognized by its cofactor; binding ligand recognized by its substrate and vice versa (i.e. biotin-

> avidin); or any permutation or combinations thereof.
>
> Among the most common molecularly recognizable portions are the three-dimensional protein arrangements in antigens of various different sorts, the cell wall structures present in various cells, . . .
>
> The second component of the system is the "molecular bridging entity". This entity need only contain a first portion capable of recognizing the molecularly on the analyte, and a second portion which comprises a polynucleotide sequence. These two portions of the bridging entity may be . . . of a different type (one being, for example, an antibody portion and the other the polynucleotide portion.)
>
> . . . If the molecularly recognizable portion on the analyte is a generalized antigen, the recognizing portion on the bridging entity should be an antibody thereto. The same is true with respect to the complementary pairs sugar/lectin, receptor/hormone, inhibitor/enzyme, and the like, previously described.

It is further disclosed in the second paragraph on page 15:

> Specific examples of bridging entities as used in this invention are covalently attached entities of monoclonal or polyclonal antibodies with polynucleotides, . . . protein antigens with polynucleotides, saccharides with polynucleotides, . . . lectins with polynucleotides, receptors with polynucleotides, hormones with polynucleotides, enzyme inhibitors with polynucleotides, enzyme cofactors with polynucleotides, and combinations and permutations thereof.

Thus, three very significant classes of polymers - polynucleotides, proteins and polysaccharides - are clearly described in full detail in the instant specification. But not only is each class of polymer itself fully described, the methods of attaching each class of polymer to other polymers are also elaborately set forth in the disclosure. In fact, Applicants devote an entire section of the specification - almost six pages - to describing the various attachments. Such attachments include, among others, the following:

- covalent attachment of polynucleotide sequences to proteins (page 23, second paragraph, through page 24, first paragraph; and page 26, first full paragraph);
- attachment of polynucleotide sequences to saccharides (page 25, first full paragraph); and
- attachment of polynucleotide sequences to other polynucleotide sequences (page 25, second full paragraph, through page 26, first paragraph).

Thus, as clearly evidenced by the foregoing discussion, generic polymers are indeed well described in the originally disclosure. The test for claim support under

the first paragraph of §112 is whether the disclosure as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support. It is indisputable that Applicants had possession of the subject matter set forth in claims 315, 321 and 328. Thus, the phrase "analog-containing polymer" recited in the claims is well supported and described in the specification.

Regarding the "clarity" of the metes and bounds of such polymers, it is respectfully submitted that having the disclosure at hand, the skilled artisan would readily understand the metes and bounds of "analog-containing polymers" set forth in claims 315, 321 and 328. Nucleic acid analogs are so well known in the art that numerous U.S. patents have issued with claims specifically reciting them as elements. Merely by way of example, the following five (5) U.S. Patents (attached as Exhibits 7-11) have issued with claim language for nucleic acid analog or nucleotide analog:

Exhibit	Patent No.	Inventor(s)	Claims	Recited Terminology
7	5,500,356	Li et al.	1	nucleotide analog
			16	nucleic acid analog
8	5,416,016	Low et al.	14, 15	nucleic acid analog or analogs
9	5,108,921	Low et al.	14, 15	nucleic acid analog or analog
10	5,055,394	Kopecko et al.	11	nucleotide analog
11	4,469,863	Ts'o et al.	1, 2-7	nucleic acid analog or analogs

Having the specification at hand, the artisan would also readily understand the metes and bounds of the "analog-containing polymer" (recited in claims 313, 319 and 321) to be the art-recognized nucleic acid analogs contained in any of the generic polymers (polynucleotides, proteins, polypeptides, polysaccharides) described in the specification, discussed *supra*.

[2] With respect to the phrase "partially double-stranded" in the claims, it is respectfully submitted that the original disclosure fully supports this language. Several portions in the disclosure point to single stranded and double stranded nucleic acid for use in accordance with the present invention. First, in describing uses ("APPLICATIONS") of the present invention, Applicants disclose on page 33,

last paragraph, through page 34, first paragraph:

> Thus, the user would utilize a cleavage method (such as use of a restriction endonuclease) to open the DNA in the first container, incorporate thereinto any desired DNA probe present in the third container or container series, ligate the polymer and then utilize the bridging entity and the signalling entity to detect and identify the presence of any desired genetic sequence present in the analyte. It should be kept in mind that a single strand cannot be cut with a restriction enzyme unless a linker (which spans the site) is first hybridized to it, thereby creating a double-strand in that location. . .

The above-quoted passage is dispositive on the issue of support for "partially double-stranded" because the double-strand is created in a location of a single strand that has been cut with a restriction enzyme. As a direct consequence easily understood by the skilled artisan, such a strand cleaved in that way would necessarily be partially double-stranded.

But other portions in the specification also support the language at hand.

The disclosure on page 11 in the specification refers to "nucleic acids or segments thereof, either single- or double-stranded" as "common analytes." Furthermore, "circular polymers of single- or double-stranded DNA" are disclosed as preferred bridging entities of the invention on page 16, second paragraph. Because it is well known in the art that single-stranded forms of nucleic acid - and not double-stranded forms - hybridize to each other through the precise alignment of complementary nucleotide bases - the skilled artisan reading the last-cited portion in the instant specification would have readily understood that double-stranded nucleic acid, segments, DNA, and the like, must be referring to partially double-stranded forms. Otherwise, hybridization as practiced in the present invention could not occur, for example, between the molecular bridging entity second portion and the signalling entity nucleic acid portion. Or, for that matter, hybridization between the molecular bridging entity first portion when it is a nucleic acid and an analyte nucleic acid.

The Federal Circuit has continued the doctrine of inherency as applied to the question of new matter. To put the doctrine into other words, an amendment that clarifies something inherent in the original disclosure does not introduce new matter. This was the conclusion reached by the Federal Circuit in the case of Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987) when it wrote:

> . . . The disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of an earlier filing date. Nor does the inclusion of a description of that property in later-filed claims change this reasonable result.
> [5 USPQ2d at 1198]

In view of the foregoing remarks and established legal principle, the recitation "partially double-stranded" must be deemed subject matter originally disclosed in this application.

[3] Regarding the specific order of complex formation in claims 365, 383, 401, and 407 (as well as claims 404 and 410 dependent therefrom), Applicants would like to point out that this issue was raised by the Examiner in the January 10, 1995 Office Action issued in their prior related application, Serial No. 08/032,769, filed on March 16, 1993. In the January 10, 1995 Office Action, the Examiner stated:

> The NEW MATTER rejection of claim 156 is reiterated and maintained as set forth in the final rejection office action mailed 8/23/94. Consideration of the arguments, filed 9/8/94, results in noting that the citation pointed to by applicants at page 61, procedure no. 15, to support present claim 156 discloses a hybridization practice, which is deemed the practice of forming complexes, as occurring concomitantly and not sequentially between the bridging entity and both the signalling entity and the target. The determinative line is "allowed to hybridize to target DNAs and to each other". Nothing in the cited phrase indicates a sequential nature to the complex formation as is presently given in claim 156. Even if applicants wish to argue that the order of wording in the above cited phrase is significant, it is noted that hybridization to the target is given first before the phrase "to each other" again lacking support for the reverse practice as given in claim 156. Additionally, the word "mixed" is present in the first line of said procedure no. 15 but this "mixed" word is not accompanied by a disclosure that hybridization occurs during the mixing. It was well known in the art at the time of the instant invention that hybridization requires appropriate conditions that are more limited and defined than simply mixing nucleic acids together. Thus, the mixing practice is not deemed to support hybridization between bridging and signalling entities prior to contact with target nucleic acid. Therefore, as stated previously, claim 156 lacks written support in the disclosure as filed. It is lastly noted that a similar rejection of claim 155 has been withdrawn because the cited support for this claim is deemed persuasive.
> [Pages 2-4 from January 10, 1995 Office Action, Serial No. 08/032,769]

For whatever reason, the arguments on the issue of complex formation have largely centered on Example 32, step no. 15, found on page 61 in the specification. Such attention has been misplaced. Although this example and step clearly support the subject matter of claims 365, 383, 401, 404, 407 and 410, the fact

remains that the specification is replete with disclosure explicitly describing complexation or hybrid formation between the signalling entity and the molecular bridging entity in advance of complexation or hybridization with the analyte.

To begin with, the embodiment of the claims at hand is described in the SUMMARY OF THE INVENTION. There, on pages 7 and 8, Applicants explicitly disclose:

> The process of the invention comprises a method of detecting in a sample an analyte (A) having a molecularly recognizable portion thereon, which comprises:
>
> providing a molecular bridging entity (B) having thereon
>
> (i) a portion capable of recognizing said molecularly recognizable portion on said analyte; and
>
> (ii) a portion comprising a polynucleotide sequence; and
>
> a signalling entity (C) having thereon
>
> (i) a polynucleotide portion capable of annealing to said polynucleotide portion of said bridging entity, thereby to form a stable polynucleotide hybrid, and
>
> (ii) a signal generating portion;
>
> forming a complex comprising:
>
> (1) said analyte (A) complexed through said molecularly recognizable portion to
>
> (2) said recognizing portion of said entity (B); said entity (B) being complexed through said polynucleotide portion thereon to
>
> (3) said polynucleotide portion of said signalling entity; and
>
> detetecting a signal by means of said signal generating portion present in said complex. [underline added]

The above-quoted disclosure also formed the *verbatim* basis for originally filed claim 1 (page 62) that immediately followed Example 32 and step no. 15 (page 61). Originally filed claim 1 recited:

> 1. A method of detecting in a sample an analyte (A) having a molecularly recognizable portion thereon, which comprises:
>
> providing a molecular bridging entity (B) having thereon:
>
> (i) a portion capable of recognizing said molecularly recognizable portion on said analyte; and
>
> (ii) a portion comprising a polynucleotide sequence; and
>
> (C) a signalling entity having thereon:
>
> (i) a polynucleotide portion capable of annealing to said polynucleotide portion of said bridging entity, thereby to form a stable polynucleotide hybrid, and

(ii) a signal generating portion;

forming a complex comprising:

(i) said analyte (A) complexed through said molecularly recognizable portion to

(ii) said recognizing portion to said entity (B); said entity (B) being complexed through said polynucleotide portion thereon to

(iii) said polynucleotide portion of said signalling entity (C); and

detecting a signal by means of said signal generating portion present in said complex. [underline also added]

Thus, it is clear from the above-quoted description (particularly the underlined portions) on pages 7-8 and the language in original claim 1 that the molecular bridging entity and the signalling entity can and do form a stable polynucleotide hybrid before the formation of the complex involving the analyte, just as set forth in claims 365, 383, 401, 404, 407 and 410.

The fact that in the present invention the molecular bridging entity and the signalling entity can and do form a stable polynucleotide hybrid in advance of any hybridization or complexation with an analyte is also explicitly described in the bridging paragraph between pages 31 and 32. In that paragraph, the following is disclosed:

> Yet another use for the process and system of the invention is in the insolubilization of analytes. Thus, if a sample is suspected of containing an analyte, and one wishes to extract and purify the analyte from the sample, the "signalling entity" is designed so that the signal generating portion comprises or is capable of specifically binding to an insoluble solid phase, such as a natural or synthetic aqueous insoluble resin, a glass, a plastic such as an acrylate or methacrylate, the inside of a test tube wall, or of a well, and the like. The bridging entity is allowed to incubate with the solid phase, thus creating recognition sites (i.e., affinity surfaces) for the analyte, which is then bound thereto.

Thus, according to the above-quoted paragraph, the signalling entity and the bridging entity are allowed to incubate and the analyte is "then bound thereto."

Example 32 in the specification also supports the subject matter set forth in claims 365, 383, 401, 404, 407 and 410. In this example, the replicative (double-stranded) form of the single-stranded bacteriophage M13 phage was used to prepare a molecular bridging entity and a signalling entity in accordance with the invention. An asymmetric DNA sequence was inserted in the replicative form to provide a molecularly recognizable portion for the molecular bridging entity. As

described on pages 57 and 58 in the specification, two single-stranded M13 nucleic acid strands were obtained that differed in polarities. One strand contained no guanylate residues of the asymmetric sequence, and was designated the G(-) strand. The other strand was designated the G(+) strand and it contained a sequence complementary to the G(-) sequence as well as guanylate residues, having not been treated with a guanosine specific reagent as in the case of the G(-) strand. The G(+) strand and the G(-) strand were used as the vector (molecular bridging entity), and the signalling entity, respectively, the latter two being recited elements in the instant claims.

When mixed in equimolar concentrations in accordance with step no. 15 on page 61 in the specification, the portions of the G(+) [molecular bridging entity] and the G(-) [signalling entity] strands which are complementary hybridized to each other under conditions sufficient to allow complexation or hybridization. In Example 32 and step no. 15, it is by virtue of the complementary sequences shared between the G(+) strand [molecular bridging entity] and the G(-) strand [signalling entity] that the two complementary strands hybridized. By the same token, the G(+) strand hybridized to the target DNA by virtue of the complementary sequences shared between that strand and the target. In this latter case, the complementary sequences were directed to the asymmetric DNA sequence inserted in the replicative form that would be used as the molecular bridging entity (the G(+) strand), and the complementary sequence in the analyte, such as a pathogenic sequence. Together with Example 32 and step no. 15, the disclosure in other portions of the specification (notably, pages 7-8, original claim 1, the full paragraph on page 28 and the bridging paragraph between pages 31-32) unambiguously support and describe the present claim language that the forming step comprises "contacting said bridging entity with said signalling entity under conditions sufficient to form a first complex and thereafter contacting the first complex with said analyte under conditions to form said complex . . ." The act of mixing recited in step no. 15 (page 61 in the specification) is just another word for "contacting" in the present claim language. As such, mixing is inextricably tied to conditions related to contacting, incubating, hybridizing and complex formation. In fact, it is possible or even likely that some degree of hybridization has occurred during the mixing step described in step no. 15 (page 61).

In the context of Example 32, the description that "[t]he (G+) and derivatized (G-) DNAs are mixed in equimolar concentration and allowed to hybridize to target DNAs and to each other" reasonably conveys the series of

events described in the preceding Paragraph 12. That is to say, the foregoing description reasonably conveys that two different hybridization events have taken place: first, that hybridization has occurred between the G(+) and G(-) strands, and second, that hybridization has occurred between the G(+) strand and the target DNA. In other words, mixing and hybridizing in step no. 15 are necessarily and inextricably related, and they do not connote separate and distinct steps as the Examiner contends.

In summary, step no. 15, taken with other portions in the specification, notably pages 7-8, original claim 1, page 28 (full paragraph) and pages 31-32 (bridging paragraph), provides irrefutable support for the specific order of complex formation set forth in claims 365, 383, 401 and 407. That is to say, the bridging entity is first contacted with the signalling entity under conditions sufficient to form a first complex that is thereafter contacted with the analyte under conditions sufficient to form the complex recited in the main independent process claims.

In addition to their above remarks, Applicants wish to point out that the law is also supportive on this issue.

The Federal Circuit has continued to maintain a consistent legal standard for new matter:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.
> [Raltston Purina Co. v. Far-Mar Co., 772 F.2d 1570, 227 USPQ 177 (Fed. Cir. 1985); In re Kaslow, 707 f.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983)]

Thus, both in law and under the facts of this case, it is altogether clear that the originally filed specification reasonably conveys to the artisan that Applicants were in possession of the subject matter of claims 365, 383, 401 and 407 at the time their application was first filed on May 5, 1983.

In light of the foregoing remarks and above amendments to the claims, it is respectfully requested that the objection and rejection under 35 U.S.C. §112, first paragraph, be withdrawn upon further consideration.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 300, 313, 315, 317-319, 321, 331, 365, 383, 401, 404, 407, and 410 stand rejected for indefiniteness under 35 U.S.C. § 112, second paragraph. In the Office Action (pages 3-8), the Examiner stated:

> [1] In claim 287, line 2, "more than one molecular bridging entity" is cited. In lines 7-8, "said bridging entity" is cited. This citation in lines 7-8 lacks antecedent basis because it directs this portion of the second part of the claimed composition to "said bridging entity" as a single item. Confusingly, there is no such "single" bridging entity described previously in the claim. Instead line 2 cites multiple bridging entities via the phrase "more than one." It is unclear which bridging entity is intended in lines 7-8 out of the multiple bridging entities cited in line 2. Lines 7-8 suggest that there is some particular bridging entity that is being referred to. Since there are only multiple bridging entities in line 2, there is no antecedent basis for the lines 7-8 citation of a particular or single bridging entity. Claims 288-290 also contain this unclarity as well as claims dependent therefrom. Clarification of this via clearer claim wording is requested.
>
> [2] Claims 283 *etc.* cites "a first part" and "a second part" wherein each "part" contains portions wherein the relationship(s) between these portions are undefined in the claims. See the below specific claim 291 explanation as an example of the unclarity in the definition of each "part" as given in the instant claims.
>
> [3] Claim 291, lines 8-9, cite "one or more polynucleotides..." but without defining their relationship to the portion that is capable of binding or hybridizing with the bridging entity. Since line 6 of claim 291 cites "a second part," this is suggestive of part (singular). Such a singular part would be expected to contain portions that are attached, linked, bound together, or related in some way. No such relationship has been defined between the two portions of the "part" of lines 6-9 of claim 291. Do applicants intend that lines 6-9 of claim 291 disclose a singular part or, alternatively, a part made up of portions which are not required to be attached or related in some way? A "part" made up of unrelated portions is vague and indefinite because this is interpretable as "parts" but is confusingly not cited in the claim as "parts". Another unclarity is that line 6 cites the second part as comprising "more than one signalling entity," each such entity comprising...," but confusingly lacks any designation of what performs the signalling function thereafter in the claim. Claims 292-294 also contain the above unclarities as well as claims dependent therefrom. Clarification is requested via clearer claim wording.
>
> [4] Claims 300 and 310 are vague and definite beyond the above unclarities in that the respective lines 1 cite "said nucleic acid" without clear antecedent basis. It is noted that several nucleic acids are given in the claims from which claims 300 and 310 depend directly or indirectly such as in the analyte in claim 299 and in the molecular bridging and signalling entities. Clarification of the claim wording is requested as to the antecedent basis.
>
> [5] Claim 322 *etc.* is vague and indefinite beyond the above unclarities in that it is unclear what the metes and bounds of the word "derived" are as cited in line 3 therein. Many other claims cite this

word also. If there are no limitations on what may be deleted, replaced, or added, such derivation may result in any other composition whatsoever. If that is so, why cite what is being altered as derived? Clarification of what is intended for such derivation practice is requested.

[6] Claim 356 lacks antecedent basis for a singular "molecular bridging entity" wherein claims 287 *etc.* cite multiple molecular bridging entities.

[7]Claims 360-362 contain the above unclarities but also are vague and indefinite as to what is meant in that claims 360-362 and claims 283, 284, 291, and 293 appear to be identical except for what the claimed subject matter is called in their respective first lines. For example, in claim 283 the subject matter is a "composition of matter" whereas in claim 360 the subject matter is an "article of manufacture." What difference is meant thereby? Does claim 360 indicate that a manufacturing process is required to prepare the claimed article whereas manufacturing is not required, is this suggestive that claim 283 includes products of nature within its scope? Clarification of the metes and bounds of each of these types of claims compared to each other is requested.

[8] Claim 438 is vague and indefinite as to what the metes and bounds are for the phrase "nucleic acid analog." Is this meant to be directed to analogs that are no longer nucleic acids but have some nucleic acid type characteristic(s)? Is this mean to be directed to nucleic acids? Aren't modified nucleic acids still nucleic acids? What differentiates nucleic acids from nucleic acid analogs? Similarly, in claim 315, line 4, the phrase "an analog-containing polymer" is cited without defining what it is an analog of. A polymer is still a polymer even if modified, isn't it? What is an analog of a polymer? Similarly, the term "modified" is given in claim 317, line 2, without defining what modifications are practicable therein. What are the metes and bounds of such modifications? Numerous instant claims contain the above unclarities and are rejected also hereinunder. Clarification is requested.

[9]Claims 364, 365, 382, and 383 cite the phrase "said complex" in their respective last lines. This "said complex" lacks clear antecedent basis because two complexes are cited that may be the antecedent. On complex is the "first complex" in line 3 of claims 364, 365, 382, and 383 and a second complex is given in line 4 of claims 363 and 381 from which claims 364, 365, 382, or 383, respectively, depend. Claim 400 contains a similar unclarity.

[10] Claims 283-438 cite the phrase "nucleic acid sequences or segments" either directly or indirectly via claim dependence. This phrase is vague and indefinite as what difference is intended between "sequences" and "segments". Since these are separately cited in the claims, this indicates that a different meaning is intended for each of these items. It is unclear what this different meaning maybe. Clarification is requested.

[11] Claims 367 and 368, lines 1-2 of each, contain the phrase "wherein said detecting step the direct" which is awkwardly worded such that it is unclear what is meant thereby. Claims 369, 371-373, 385-387, and 389-391 also contain similar confusing wording.

[12] Claims 374 and 392 are vague and indefinite due to unclarity of what is meant by the phrase "and a binding step on an insoluble phase." Is this intended to indicate that a binding step is present only within the detecting step of the process or is this

> intended to indicate that the binding may occur anywhere in the process? It is noted that claim 65, as filed, as pointed to by applicants indicates that the detecting step per se is limited to comprise a binding step on an insoluble phase. Clarification is requested.
>
> **[13]** Claims 343-346 are vague and indefinite because it is unclear what is meant by citing the word "indirectly" twice in the last line of claim 343. Does this indicate that at least two linkages are required between the signalling entity and the actual signal producing entity? Or some other indirect procedure? Clarification is requested.

The indefiniteness rejection is respectfully traversed.

In order to ensure that each and every matter raised in the indefiniteness rejection has been thoroughly addressed, Applicants have inserted bold bracketed numbers above. Each bracketed number will be handled in turn below.

[1] Regarding the antecedent basis for "said bridging entity" in claims 287-290, all of these claims have been amended by inserting the phrase "more than one" before the "bridging entity nucleic acid second portion." it is believed that those amendments removes renders moot this issue of indefiniteness.

[2] With respect to the recitation of "a first part" and "a second part" in claims 283 *etc.*, Applicants would like to draw attention to the fact that such terminology has been long accepted as appropriate and definite in U.S. patent practice. In fact, in their April 12, 1996 Second Preliminary Amendment (page 31, last paragraph, through page 32), Applicants addressed the matter of claiming a composition of matter as a first part, second part, etc. For the sake of completeness as well as for the Examiner's convenience, those remarks from Applicants' April 12, 1996 Second Preliminary Amendment are reiterated:

> In addition, independent composition claims 283, 284, 287, 288, 291 and 293 (as well as the claims depending therefrom) recite a composition of matter in either two parts or three parts. These claims were also drafted in accordance with the April 3rd interview in which "[t]he possibility of a composition claim with possibly separate parts was discussed." See April 3rd Interview Summary Record. The basis for claiming a composition of matter in more than one part is well established in U.S. patent practice. Representative are the following eleven (11) U.S. patents in which claims have issued with similar, if not identical, language as in the instant composition claims. For the Examiner's convenience, a copy of each of these patents has been attached as Exhibits 1-11, respectively.

Exhibit No.	Inventor	U.S. Patent No.	Claims/Recitation
1	Palmer et al.	5,246,980	claim 1 ("two part composition")

2	Wollard	5,212,231	claims 21-34 ("two-part curable liquid polysulphide resin composition")
3	LeCompte et al.	5,128,433	claim 1 ("two-part composition")
4	Beale	5,096,497	claim 1 ("two part composition")
5	Liu	5,079,098	claims 1-20 ("two-part composition")
6	Chanen et al.	5,068,114	claim 1 ("two space part composition) claim 16 ("three-space part composition")
7	Okamoto et al.	5,066,743	claims 1-25 ("two-part composition")
8	Baines et al.	5,026,542	claims 1-6 ("two part composition")
9	Boettcher	4,168,363	claim 1 ("two-part composition")
10	Goudie et al.	4,083,951	claims 18-19 ("composition as claimed in claim 11 in the form of a two-part unit-dose composition")
11	Groves et al.	4,060,583	claims 1 and 7 ("two-part composition")

Accordingly, the "first part," "second part," and "third part" recitation in any of the claims 283, 284, 287, 288, 291 and 293 is fully supported both in the original disclosure and under U.S. patent practice as evidenced by the above submitted U.S. patents (Exhibits 1-11).

The eleven U.S. patents submitted as Exhibits 1-11 in Applicants' April 12, 1996 Second Preliminary Amendment are, of course, attached to that paper. A review of those eleven U.S. patents (Exhibits 1-11) fails to reveal any cooperativity between the claimed composition parts beyond any expressed in the instant claims. In fact, it is the very nature of claiming composition as separate parts that little or no cooperativity is required.

[3] With regard to the relationship of the "one or more polynucleotides" recited in claims 291-294, it is believed that the amendments to these claims effectively removes any ambiguity in the claim language. Each of claims 291-294 has been amended by inserting the phrase "capable of providing a detectable signal" after "one or more chemically modified or artificially altered polynucleotides." By having amended these claims in that way, it has been made clear that the signalling function in the detection process is performed or carried out by means of the one or more chemically modified or artificially altered polynucleotides.

[4] In response to the Examiner's request, clarity in claims 300 and 310

has been imparted by inserting in the former claim the term "analyte" before "nucleic acid" and by inserting in the latter claim, the phrase "molecular bridging recognizing first portion" before "nucleic acid."

[5] With respect to the term "derived" in claims 322, *etc.*, it is believed that this term is properly disclosed and supported by the original disclosure. The language in claim 322 recites "wherein said nucleic acid sequences or segments in the molecular bridging entity second portion is derived from a phage selected from the group consisting of a T even phage, a filamentous phage, an M13 phage, or an M13 variant." Claim 334 contains similar language but directed to the signalling entity nucleic acid portion that is "derived from a phage selected from the group consisting of a T even phage, a filamentous phage, and an M13 phage, or an M13 phage variant." It is clear from the precise language of both claims that the term "derived" refers to nucleic acid that could be derived from any of those phage listed as Markush members. Because the identity of those phage members have been well characterized in the art, the skilled artisan would certainly understand in reading the two claims at hand that the nucleic acid that can be incorporated into either the molecular bridging entity second portion or the signalling entity nucleic acid, or both, is derived (or obtained or taken) from such phage. The term "derived" is specifically directed to those phage members recited in claims 322 and 334. Thus, it would be patently clear to the artisan what is intended by ther term "derived" in both claims.

Beyond the clear meaning of the language in claims 322 and 334, Applicants would like to bring attention to the fact that the term "derived" is well accepted in patent parlance, having been recited so frequently in issued U.S. patent claims that it would be a tremendous burden just to list these documents whose numbers would run well into the hundreds and moreover, even into the thousands!. Its recitation in various claims is, therefore, proper under the law and in U.S. patent practice. Literally thousands of U.S. patents have issued with language similar if not identical to that in claims 322 or 334. In fact, a recent search of a well known computer database has revealed that more than 50,000 U.S. patents have been issued with the term "derived" in the claims! Linking the term "derived" to any of "nucleic acid," "nucleotide," "oligonucleotide" or "polynucleotide" provided more than two hundred (200) hits, of which twenty-seven (27) belong to the instant assignee or related company. Even when limited to more specific language, such as nucleic acid derived and oligonucleotide or polynucleotide derived, there are several U.S. patents that have been issued with such claims. Just to illustrate this point,

the following five (5) U.S. patents (and there are many more than those listed) have been issued:

Exhibit	Patent No.	Inventor(s)	Claims	Recited Terminology
12	5,599,922	Gryaznov et al.	15	polynucleotide . . . derived
13	5,582,986	Monia et al.	1	oligonucleotide . . . derived
14	5,573,925	Halazonetis	5,11	nucleotide . . . derived
15	5,556,747	Kumar	7, 8	DNA molecule derived
16	5,529,926	Maat et al.	5,6	nucleotide . . . derived

Finally, Applicants' attorney was unable to find any precedential caselaw that would prohibit or preclude the use of the term "derived" as being indefinite under the second paragraph of 35 U.S.C. §112. Accordingly, the use of this term is believed to be proper under the law.

[6] Regarding the lack of antecedent basis in claim 356, as discussed in the opening remarks of this Amendment, this claim has been amended to recite "wherein the ratio of signalling entities to molecular bridging entities is greater than 5." In light of that amendment to claim 356, it is believed that this issue has been rendered moot.

[7] Concerning the claiming of a composition of matter (for example, claim 283) and an article of manufacture (for example, claim 360), it is believed that such claimed subject matter is altogether proper under the law and under U.S. patent practice. 35 U.S.C. §101 provides that "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." Thus, the language of §101 recognizes manufactures (that is, articles of manufacture) as a separate and patentable class of subject matter from compositions of matter.

Beyond that, the U.S. Patent Office has always operated on the assumption that an article of manufacture and a composition of matter are separate and patentable classes of subject matter. Beginning with §706.03(a) [Rejections under 35 U.S.C. 101] in the Manual of Patent Examining Procedure (MPEP), examiners are advised:

> Patents are not granted for all new and useful inventions and

> discoveries. The subject matter of the invention or discovery must come within the boundaries set forth by 35 U.S.C. 101, which permits patents to be granted only for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.
>
> [MPEP, page 700-29, Rev. 2, July 1996]

And that recognition by the Patent Office has certainly been reflected in numerous U.S. patents that have issued in which a composition of matter and an article of manufacture are claimed in the same document and even in some instances in the very same claim. With respect to a composition of matter and an article of manfacture being claimed in the same document, the following U.S. patents are representative but by no means exhaustive:

Exhibit	Patent No.	Inventor(s)	Subject Matter	Reference Claims
17	5,561,220	Dean et al.	composition	19-21
			article of manuf.	11-13
18	5,556,892	Pekala et al.	composition	1
			article of manuf.	3
19	5,532,350	Cottrell et al.	composition	1
			article of manuf.	15, 24
20	5,221,794	Ackerman et al.	composition	6
			article of manuf.	12
21	5,156,804	Halverson et al.	composition	1, 12-13
			article of manuf.	10
22	5,149,435	Laube	composition	19
			article of manuf.	15

And for those U.S. patents with at least one claim reciting both a composition of matter and an article of manufacture, the following are non-limiting examples:

Exhibit	Patent No.	Inventor(s)	Subject Matter	Reference Claims
23	5,483,010	Anderson et al.	composition/article	10

24	5,454,999	Jayashankar et al.	composition/article	11
25	5,340,531	Jayashankar et al.	composition/article	7
26	5,338,827	Serafini et al.	composition/article	21-22
27	5,286,446	McGarry	composition/article	4-6
28	5,149,772	Serafini et al.	composition/article	23-24

[8] With respect to the metes and bounds for the phrase "nucleic acid analog" recited in claim 438, Applicants respectfully point out that such usage is altogether proper and meets the statutory strictures for definiteness. As indicated in response to the objection and rejection under 35 U.S.C. §112, first paragraph, several U.S. patents have been issued with similar if not identical language as "nucleic acid analog." The five patents listed above and attached as Exhibits 7-11 are dispositive on the point that "nucleic acid analog" recited in claim 438 meets the statutory strictures for definiteness.

Beyond that, Applicants would like to point out that "nucleic acid analog" is well accepted and often used terminology in the art, that has come to mean those nucleotides which are structurally similar to the nucleotides having the oft-mentioned bases, adenine, thymine, guanine, cytidine and uracil. Several published review articles refer to nucleic acid analogs in one form or another, including the following:

Banerjee, "5'-Terminal Cap Structure in Eucaryotic Messenger Ribonucleic Acids," Microbiological Reviews 44:175-205 (June 1980) [copy attached as Exhibit 29];

Oberg et al., "The Relative Merits and Drawbacks of New Nucleoside Analogues with Clinical Potential," Journal of Antimicrob. Chemother. 14:5-26 (August 1984) [Exhibit 30];

Larkins et al., "Molecular Mechanisms Regulating the Synthesis of Storage Proteins in Maize Endosperm," Critical Reviews in Food Science and Nutrition 16:199-215 (1982) [Exhibit 31]; and

Shatkin et al., "5'-Terminal Caps, Cap-Binding Proteins and Eukaryotic mRNA Function," Biochem. Soc. Symp. 47:129-143 (1982) [Exhibit 32].

It is respectfully submitted, therefore, that the phrase "nucleic acid analog" in the instant claims is proper and definite.

Applicants also acknowledge the Examiner's comments regarding the recitation of the term "modified" in claim 317, line 2. Claim 317 recites "wherein said oligo- or polynucleotide comprises a modified oligo- or polynucleotide." The term "modified" is also recited in connection with "one or more polynucleotides" in claims 291-294, 312, 318, 329, 330, 335-336, 339, 343, 347, 350, 353, 361, 405, 416-417, 427, 435 and 438. The use of the term "modified" in all of these claims is proper under the statute. This issue was actually addressed earlier by Applicants in their March 5, 1996 Preliminary Amendment. That response was also directed to an indefiniteness rejection. For the Examiner's convenience, those earlier remarks taken from pages 36-37 of Applicants' March 5th Preliminary Amendment are reiterated below:

> Turning to the word "modified" as applied to "oligo- or polynucleotide" in the new claims above (167, 172, 182, 187-188, 219, 224, 234 and 239-240), Applicants note at the outset that modified nucleotides and polynucleotides containing such modified nucleotides are disclosed in U.S. Patent Nos. 5,328,824; 5,449,767; 5,476,928; 4,711,955; and 5,241,060, all of which have been incorporated by reference into the instant application. See page 20, last paragraph, through page 21, first paragraph of the instant specification. See also this Amendment, page 2, last paragraph, through page 3, first paragraph. Furthermore, in the specification (page 21, full paragraph), Applicants provide a discussion of other natural biologically modified polynucleotides which can be used in accordance with the instant invention. Applicants would respectfully like to point out that the term "modified" as applied to nucleic acids, oligonucleotides, polynucleotides, and the like, is both recognized and accepted in the art. A number of U.S. patents have issued over the years with claims having similar if not identical language to the language at issue here. These patents include but are not limited to the following six (6) patents:

Exhibit No.	Patent No.	Inventor(s)	Recited Terminology/Claims
2	5,270,184	Walker et al.	modified nucleotide (claims 1-14)
3	5,124,246	Urdea et al.	modified nucleotides (claim 9)
4	5,093,232	Urdea et al.	modified nucleotide (claims 1-14)

5	4,987,065	Stavrianopoulos et al.	modified nucleic acid base (claims 1-3) modified base (claims 13-15, 20-21 & 23)
6	4,948,882	Ruth et al.	modified nucleoside monomer (claims 3-4)
7	4,835,263	Nguyen et al.	modified chain of nucleotides (claims 1 & 3-6)

A copy of each of the above-listed six (6) patents are attached hereto as Exhibits 2-7. It is respectfully submitted that the instant use of the expression "modified oligo- or polynucleotide" is altogether proper and appropriate under the law as evidenced by the issuance of a vast number of patents with similar phraseology. Applicants earnestly request that the instant usage be given similar deference as in the case of these other issued U.S. patents.

In view of Applicants' remarks reproduced from their March 5, 1996 Preliminary Amendment and the seven U.S. patents attached thereto, it is believed that the use of the term "modified" in connection with oligo- or polynucleotide is altogether proper and definite under the statute.

[9] Regarding the antecedent basis for "said complex" in various process claims, it is believed that the above amendments to the claims obviates this ground for rejection. In claims 364-365, 382-383 and 400-401, the phrase "recited in said forming step" has been added to the end of each claim. In this way, the claim language has been made clear to the reader that the complex formed "thereafter" is the same complex recited in said forming step.

[10] Respecting the phrase "nucleic acid sequences or segments" in the instant claims, Applicants would like to point out that such language is proper and definite under the statute. The terminology "nucleic acid sequence" is, of course, well-accepted in the art, and in fact, it can also be found as a definition in various scientific dictionaries. For example, in Stenesh's Dictionary of Biochemistry and Molecular Biology (Second Edition, John Wiley & Sons, New York, 1989), the term "sequence" is defined on page 437 as:

> 1. The linear order in which monomers occur in a polymer; the order of amino acids in a polypeptide chain, and the order of nucleotides in a polynucleotide strand are examples.

A copy of Stenesh's definition is attached as Exhibit 33.

It is believed that the term "nucleic acid segment" is equally well-accepted in

the art, and is functionally equivalent but not necessarily identical to "nucleic acid sequence." A nucleic acid segment contains, of course, a nucleic acid sequence or sequences. And, of course, a nucleic sequence or sequences could be considered as a nucleic acid segment.

[11] As indicated in the opening remarks of this Amendment, direct detection as a process step has been clarified in claims 366-369, 371-373 and 385-387. In view of the amendments to these claims, it is believed that the issue with respect to the phrase "wherein said detecting step the direct" has been obviated.

[12] As noted above, the phrase "a binding step on an insoluble phase" has been deleted as a Markush member from claims 374 and 392, and has been incorporated into new claims 439 and 440. The latter two claims conform to the language in original claim 65 that originally recited "a binding step on an insoluble phase. By clarifying the claims as requested by the Examiner, this ground is believed to have been obviated.

[13] As in the case of claims for direct detection (366-369, 371-373 and 385-387), claims for subject matter in which indirect detection is carried out have been clarified in response to the Examiner's request. The affected claims include 343-346, 370-373 and 388-391. In view of the above amendments to the foregoing claims, it is believed that this issue has been satisfactorily handled.

In view of the above amendments to the claims, the statutory requirements for definiteness, and the attached exhibits (12-33), Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Commonality of Ownership

Pursuant to their obligation under 37 C.F.R. §1.56, Applicants and their attorney confirm that the subject matter embraced by the presently pending claims were and continue to be commonly owned.

The Rejection Under 35 U.S.C. §102

Claims 283-296, 298-301, 304, 307, 309-321, 323-333, 335-340, 347, 350, 353, 358-364, 366, 367, 372-376, 378-382, 384, 385, 392-394, 396-400, 402, 403, 406, 408, 409 and 438 stand rejected under 35 U.S.C. §102(b) as being clearly anticipated by Dunn et al. ["A Novel Method to Map Transcripts: Evidence for Homology between an Adenovirus mRNA and Discrete Multiple Regions of the Viral Genome," Cell 12:23-36 (1977)]. In the Office Action (pages 8-9), the Examiner stated:

> Dunn et al. read on the above-listed claims due to its disclosure of an immobilized target analyte wherein a bridging entity is hybridized thereto followed by washing and then the hybridization of a nick translated radiolabelled signalling entity that is made up of a heterogeneous mixture of radiolabelled fragments produced as a result of the nick translation process. This nick translation process also results in a ration of signalling entities as being clearly greater than 1 as compared to bridging entities, but is unclear how much greater than 1.

The anticipation rejection is respectfully traversed.

Before addressing this rejection, some introductory remarks are in order.

Robert L. Harmon has provided one of the best summaries on the law of anticipation in his treatise, Patents and the Federal Circuit [3rd edition, The Bureau of National Affairs, Inc., Washington, D.C., 1994, Chapter 3, "Novelty and Loss of Right]. On the general test for anticipation, Mr. Harmon writes:

> The Federal Circuit has spoken clearly and at some length on the question of anticipation. At the outset, it warns us that anticipation as used in the case law prior to the Patent Act of 1952 may not have been used in the sense it is today (citation omitted). **Under modern decisions, anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference**[4] or embodied in a single prior art device or practice.[5] **Those elements must either be inherent or disclosed expressly**[6] **and *must be arranged as in the claim***.[7] For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.[8]
>
> [Patent and the Federal Circuit, pages 57-58, citations omitted and emphasis added]

Equally good is Irah H. Donner's anticipation discussion in his treatise, Patent Prosecution: Practice & Procedure Before the U.S. Patent Office [The Bureau of

National Affairs, Inc., Washington, D.C., 1996, Chapter 6, "Anticipation Standard Under 35 U.S.C. Section 102"]:

> According to the Federal Circuit, "[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration."290 It is not enough, however, that the reference disclose all the claimed elements in isolation. Rather, as stated by the Federal Circuit, the prior art reference must disclose each element of the claimed invention "*arranged as in the claim*."291 Thus, even if the prior art reference includes all the elements that are claimed, if the arrangement of the claimed elements is different from the arrangement of the prior art elements, anticipation will not be present.
>
> Anticipation will not be found in a situation where the claimed elements are arranged differently in the prior art. Further, anticipation will not be found when the prior art is lacking or missing a specific feature or the structure of the claimed invention.
>
> [Patent Prosecution, page 323]

An examination of the instantly claimed invention against Dunn's disclosure - and taken in light of the foregoing legal principles - clearly establishes that the anticipation rejection cannot be sustained and should be withdrawn.

As exemplified in claim 283, the instant claims are directed to a two-part composition in which the first part comprises a first portion capable of recognizing and binding to or hybridizing with a molecularly recognizable portion on an analyte, and a second portion comprising one or more nucleic acid sequences or segments. The second part comprises one or more signalling entities substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte, each such entity comprising a nucleic acid portion capable of binding to or hybridizing with said bridging entity nucleic acid second portion, and one or more signal generating portions capable of providing a detectable signal. Thus, the instantly claimed invention eschews any or all notion of the sandwich hybridization technique disclosed in Dunn et al.

It is unmistakably clear that the anticipation rejection based upon Dunn et al. cannot be maintained in light of the above-quoted legal principles. First, the anticipation rejection is inappropriate because Dunn et al. fail to disclose at least two essential material elements in the instantly claimed invention. Beyond that, Dunn et al. fail to disclose these two elements as arranged in the instant claims, another clear requirement under the law. In addition to lacking two instantly claimed material elements and their arrangement in the claims, Dunn et al. lack any notion of the universality of the present invention, and furthermore, they fail to

place Applicants' invention in the hands of the public.

One essential material claim element that is clearly lacking in Dunn et al. are signalling entities that are capable of binding to or hybridizing with one or more molecular bridging entities. In sandwich hybridization as disclosed in Dunn et al., both the immobilized adenovirus type 2 DNA (the capture probe) and the ^{32}P-labeled SV40 DNA (the signalling probe) are complementary to the target polyribonucleotide. In other words, Dunn's two probes in the sandwich hybridization technique each hybridize to different portions of the target RNA - and not to each other. In contrast, the instantly claimed invention specifically recites that the molecular bridging entity and the signalling entity are capable of binding to or hybridizing with each other through their respective nucleic acid portions.

A second material element clearly lacking in Dunn et al. is the requirement now present in the claims that the signalling entity or entities be substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte. As discussed *supra* (see this Amendment, page 31, last paragraph, through page 32, penultimate paragraph), this second limitation in the instant claims clearly removes altogether the present invention from the sandwich hybridization technique disclosed in both the Dunn and Ranki documents, both of which are cited of record. Without both of these elements in the cited disclosure, the anticipation rejection based upon Dunn et al. cannot be sustained. In the case of Dunn et al. only an analyte-specific radioactively labeled polynucleotide tail is disclosed and used. To assert that Dunn et al. reads on the instant claims "due to its disclosure of an immobilized target analyte wherein a bridging entity is hybridized thereto followed by . . . hybridization of a signalling entity . . . " ignores the clear and precise disclosure of the cited document that clearly says otherwise. What is disclosed in Dunn's article is a sandwich hybridization technique involving naturally occurring RNA transcripts. In the sandwich hybridization technique employed by Dunn et al., the target adenovirus RNA is sandwiched between an immobilized adenovirus type 2 probe, and a radioactively labeled ^{32}P fragment of viral DNA, the latter hybridizing to "tail" sequences found on the analyte - which are not found on the probe or some other entity.

That the "analyte" in Dunn et al. was and could only be the adenovirus RNA is clearly evidenced by their disclosure. Dunn et al. were only seeking to map RNA transcripts whose presence was known but whose location on the viral genome was not known. Thus, the unknown (or in other words, the "analyte") in Dunn's

case could only be the adenovirus RNA, because the authors had previously obtained by isolation the adenovirus type 2 DNA that they had immobilized on nitrocellulose filters. That this is plainly so is seen in the following portions in Dunn et al.:

First, the very title of Dunn's article is "*A Novel Method to Map Transcripts*: Evidence for Homology between an Adenovirus mRNA and Discrete Multiple Regions of the Viral Genome." [emphasis added]

Second, Dunn's summary at the beginning of the article explains: "A method has been devised which permits mapping of transcripts by a two-step hybridization procedure (sandwich hybridization)." [emphasis added]

Third, Dunn's introduction on the first page of the article again emphasizes naturally occurring mapping transcripts: "Several approaches to mapping the regions of adenovirus type 2 (Ad2) DNA which are transcribed have been developed in recent years." [emphasis added]

Later on the first page, the authors explain: "By using DNA radioactively labeled to high specific activity in vitro as a probe, we have overcome some of the limitations to mapping RNA labeled in vivo." [emphasis added]

In describing their procedure, also on page 23, right column, Dunn et al. write:

> An outline of the procedure we have used to map viral RNAs comprised of both SV40 and Ad2 sequences is shown in Figure 1B. Ad2 DNA is cleaved with a restriction endonuclease, the resulting fragments separated by agarose gel electrophoresis and transferred to a nitrocellulose filter (Southern, 1975). **Unlabeled RNA [analyte] extracted from cells** lytically infected with an adenovirus-SV40 hybrid is hybridized to the immobilized DNA fragments, the filters are washed to remove unannealed RNA and hybridization is continued with SV40 DNA that has been labeled in vitro with ^{32}P to high specific activity (citations omitted). After again washing the filters, the Ad2 DNA fragments complementary to RNA which contains SV40 sequences can be identified by autoradiography. We have in this way **demonstrated the existence of an RNA molecule consisting of Ad2 and SV40 sequences in one continuous chain** and have mapped the location of the sequences which serve as template for its synthesis on the Ad2 + ND1 genome. [parenthetical added]

The RNA molecule whose existence was sought to be demonstrated by Dunn

et al. was and could only have been an analyte. And Dunn's analyte RNA molecule consisted of adenovirus and SV40 sequences in one continuous chain. In fact, Dunn et al. highlight this feature of their disclosure when writing on the first page of their cited 1977 Cell article:

> . . . We have in this way **demonstrated the existence of an RNA molecule consisting of Ad2 and SV40 sequences *in one continuous chain*** and have mapped the location of the sequences which serve as template for its synthesis on the Ad2 + ND1 genome. . .
> [Dunn et al., Cell 12:23 (1977); left column, last paragraph; emphasis added]

In sharp contrast to Dunn's disclosure, the analyte in the present invention could never have in one continuous chain the complementary sequences corresponding to both the molecular bridging entity and the signalling entity for the very clear and simple fact that the latter is substantially incapable of binding to or hybridizing with the analyte.

And in Figure 1B on page 24, specifically, the lower right portion, Dunn et al. provide an illustration of their sandwich hybridization technique. The illustration clearly depicts adenovirus RNA and its natural SV40 RNA tail sandwiched between immobilized Ad2 DNA and SV40 ^{32}P-labeled DNA, the latter two being of course, capture and signalling probes, respectively. Dunn's illustration in Figure 1B is nothing more than and nothing less than a rendition of the format later adapted by Ranki in which two probes - both probes being noncomplementary to each other and one probe being radiolabeled - hybridize to different sequences in the target analyte polynucleotide. See Ranki et al., U.S. Patent No. 4,486,539, issued on December 4, 1984, already of record in this application.

The most telling and accurate characterization of Dunn and Hassell's disclosure, however, comes from the authors themselves - even years after their cited 1977 Cell paper.

One year later, the lead author Dunn characterized his 1977 work in precisely the same way as that work was itself first presented, namely, as a sandwich hybridization for RNA transcript mapping:

> . . . The first of these, sandwich hybridization (Dunn and Hassell, 1977), depends upon the fact that of the late RNAs present, only the hybrid RNAs contain both SV40 and adenoviral sequences. Thus, when the hybrid mRNAs (or a cDNA copy of them) are **hybridized to**

> **defined fragments of adenoviral DNA bound to nitrocellulose filters**, they form duplexes through their adenoviral sequences, leaving their SV40 sequences as protruding tails. The process of annealing with ^{32}P-labeled SV40 DNA causes these tails to become labeled, permitting autoradiographic identification of the sequences of adenovirus 2 which are homologous to the hybrid mRNA.
>
> [Dunn et al., "A Supplementary Adenoviral Leader Sequence and Its Role in Messenger Translation," Cell 15:511-526 (1978); emphasis added; copy attached as Exhibit 34]

Three years later, the lead author Dunn is still characterizing his own 1977 paper in the same identical way, that is, the use of sandwich hybridization to map viral mRNAs using a DNA probe in the form of a DNA fragment immobilized to a nitrocellulose filter:

> Messenger RNAs are most commonly assigned to specific genomic locations by demonstrating that they are complementary to a restriction fragment of DNA whose position within the genome is known. Hybridization to two adjacent fragments is usually taken to mean that a particular mRNA contains sequences which are contiguous within the genome and which span the restriction endonuclease cleavage site. However, this conclusion is fragile because the possibility exists that the mRNA preparation contains two or more species which happen to be complementary to adjacent genomic fragments. In eukaryotic systems, the interpretation is clouded because mature mRNAs generally are spliced and consist of sequences derived from noncontiguous genomic regions. The technique of sandwich hybridization[1] eliminates some of these problems, and it provides a biochemical method to determine whether sequences from different regions of a genome are covalently joined to one another in mRNA.
>
> In theory, the technique is of general application and can be used to analyze the transcription products of any segment of DNA whose restriction maps are known. . .
>
> [1] A. R. Dunn and J. A. Hassell, *Cell* **12**, 23-36 (1977).
>
> [Dunn and Sambrook, "Mapping Viral mRNAs by Sandwich Hybridization," Methods in Enzymology 65:468-478 (1980); copy attached as Exhibit 35]

It should not be overlooked that Dunn's 1980 article was published in Methods of Enzymology, a techniques journal directed to practical applications. The most practical application of Dunn's sandwich hybridization - and in fact, the only practical application at that time - was to map RNA transcripts.

Given considerable time (as much as three years or more) to reflect on his 1977 Cell paper and, furthermore, given the opportunity to expand on its potential

impact as a "model system," what does author Dunn do? He characterizes the work in the same identical way as it was originally presented as a paper in 1977, confining it to:

- viral RNA transcript mapping

and

- using sandwich hybridization.

Given multiple opportunities and substantial time to reflect and expand upon their 1977 publication, Dunn et al. could do no more than to describe their work in terms of those three aforementioned elements: viral RNA transcript mapping using sandwich hybridization.

Needless to say, the literature is replete with descriptions and definitions for sandwich hybridization including Dunn and Hassell's role in its development.

It is wholly significant that in the first edition of their book DNA Probes George H. Keller and Mark M. Manak write about the very same Dunn and Hassell 1977 article cited in the instant anticipation rejection:

> The sandwich hybridization format was originally described by **Dunn and Hassell (1977)** and adapted by Ranki *et al.* (1983) and Ranki and Soderlund (1984). It was developed to avoid the tedious purification and immobilization of sample nucleic acid required in most solid phase hybridization formats. Sandwich hybridization has two main advantages over direct filter hybridization, sample immobilization is not required and crude samples can be assayed reliably. In addition, sandwich hybridization is potentially more specific than direct hybridization because two hybridization events must occur in order to generate a signal. Solid phase sandwich hybridization requires two adjacent, non-overlapping probes; **an immobilized capture probe and a labeled detection probe**. Figure 5.8 illustrates a typical sandwich hybridization scheme consisting of an **immobilized capture sequence** cloned into M13 and **an adjacent detection sequence** cloned into pBR322. A sandwich structure can form only if the sample contains nucleic acid which spans the original junction between the two fragments in genomic nucleic acid. . .
> [DNA Probes, Stockton Press, New York, 1989, Section Five: *Hybridization Formats and Detection Procedures*, pages 198-199; copy attached as Exhibit 36; emphasis added]

The same description was repeated by Keller and Manak in the much expanded Second Edition of DNA Probes. See pages 238-239 from DNA Probes, 2nd edition, Stockton Press, New York, 1993, Section Six: *Hybridization Formats*

> The sandwich hybridization assay (Figure 2-3) is a modification of the dot/blot hybridization assay and was designed to overcome the problem of nonspecific signal generated with crude samples. The assay requires the purification of two nucleic acid reagents. These sequences are adjacent to one another in the target of interest, but are noncomplementary. **One sequence, known as the "filter" or "target" probe, is immobilized on the membrane. The other sequence is the labeled, or detection, probe**. The crude sample is interacted with the filter and detection probes simultaneously. Only samples with sequences capable of forming a "sandwich" between the target and probe sequences will generate a signal. . .
> [Nucleic Acid Probes: A Primer for Pathologists, American Society of Clinical Pathologists, Chicago, 1989, Chapter 2, Nucleic acid hybridization analyses and other nucleic acid assays, pages 49-50, copy attached as Exhibit 40, emphasis added]

And in Nucleic Acid Probes edited by Robert H. Symons, Ph.D, two-phase sandwich hybridization is described thusly:

> This method was developed by Ranki et al.[102] for the detection and quantitation of nucleic acids in crude clinical samples using adenovirus DNA as a model.[103] As far as we are aware, it has not been used for the detection of plant virus nucleic acids. The general principle of the method is outlined in Figure 5A using nonradioactive single-stranded DNA probes in the phage M13 DNA vector as an example. Two probes are required which hybridize to different, nonoverlapping regions of the target nucleic acid. One probe is bound to a solid support such as nitrocellulose by standard procedures while the other is labeled . . . The probe-bound filter is hybridized with the test nucleic acid sample in the presence of the second biotin-labeled probe which can only be bound to the filter via the bridge of target nucleic acid. . .
> [Nucleic Acid Probes, CRC Press, Inc., Boca Raton, FL, 1989, Chapter 4, Nucleic Acid Probes in the Diagnosis of Plant Viruses and Viroids, J. L. McInnes and R. H. Symons, page 130, copy attached as Exhibit 41]

All of the above listed descriptions and definitions are consistent with Ranki's definition as well as being consistent with each other and with the art-recognized and art-accepted usage of the term "sandwich hybridization."

The Ad2 DNA that Dunn et al. immobilized to nitrocellulose filters for the purpose of mapping RNA transcripts was isolated from purified virions. See the "Experimental Procedures" at the end of the article, page 34, right column under "Isolation of Viral DNA." Its identity and presence were clearly known. It was and could not in any way be termed an "analyte" under any circumstance, definition or analysis.

Even if Dunn et al. obtained a heterogenous mixture of radiolabelled fragments produced as a result of the nick translation process, the fact remains that they did not produce the instantly claimed composition. As discussed above, Dunn's was a sandwich hybridization in which the radiolabelled SV40 DNA was specific only to the target adenovirus RNA. The instant composition is directed to one or more specific signalling entities substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte. As such, the instant composition is not a sandwich hybridization a la Dunn et al., each of which comprises a nucleic acid portion capable of binding to or hybridizing with the instantly recited analyte-specific molecular bridging entity, and one or more signal generating portions capable of providing a detectable signal. In Dunn's case, their SV40 ^{32}P labeled DNA was specific only to the target adenovirus RNA.

Finally, on the issue of anticipation, the newly added process claims directed to the use of "one or more signalling entities" are also deemed to be wholly outside of Dunn's disclosure. As discussed *supra* (see this Amendment, page 33, last paragraph; and page 62, last paragraph, through page 66, first full paragraph), Dunn and Hassell never performed or even contemplated any detection of an unknown analyte. All of their 1977 disclosure as well as subsequent related disclosures (see, for example, their 1978 Cell paper and their 1980 Methods in Enzymology publication, both cited and discussed *infra* (see the remarks in the obviousness rejection below) only concerned RNA transcript mapping in which the presence of each and every elements has been predetermined. Transcript mapping stands in stark contrast to detecting unknown analytes in a sample. The former cannot in any way be a predicate for success in the latter.

To recapitulate, a comparison between Dunn's disclosure and the instantly claimed invention shows a distinct lack of identity in material elements:

Dunn et al.	Present Invention
two probes hybridize to different portions of analyte and not to each other	molecular bridging entity and signalling entity hybridize to each other by virtue of complementary nucleic acid portions
^{32}P-labeled DNA probe hybridizes to target RNA analyte	signalling entity is substantially incapable of binding/hybridizing to analyte

analyte RNA sequences complementary to immobilized Ad2 DNA probe and ^{32}P-labeled SV40 DNA probe lie in one continuous chain	analyte sequences can never lie in one continuous chain because signalling entity is substantially incapable of binding/hybridizing with analyte
no universal concept - confined to RNA transcript mapping	provides universal concept and system (applicable to universal array of analytes and the signalling entities can be universally used regardless of molecularly recognizable analyte portions)

In short, the rejection of the instant claims as being anticipated by Dunn et al. cannot be maintained. First, Dunn et al. do not identically describe the claimed invention at hand. Second, Dunn et al. do not enable one skilled in the art to practice the "universal" invention as set forth in the instant claims and as disclosed in Applicants' specification. Third, Dunn's disclosure does not place Applicants' claimed invention in the possession of the public.

In light of its disclosure and the foregoing legal principles, it is respectfully submitted that the anticipation rejection by Dunn et al. cannot be reasonably maintained. The withdrawal of this rejection is respectfully urged.

The Rejection Under 35 U.S.C. §103

Claims 283-301, 304, 307, 309-340, 343-364, 366, 367, 370-376, 378-382, 384, 385, 388, 390-394, 396-400, 402, 403, 405, 406, 408, 409, 411, 414, 416, 418-438 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dunn et al. (1977), *supra*, taken in view of Ward et al., U.S. Patent No. 4,711,955. In the Office Action (pages 10-11), the Examiner characterized the presently claimed invention as the following:

> The instant invention is directed to compositions for detecting an analyte via the recognition and binding of a bridging entity to the analyte. The bridging entity contains two portions, one portion that recognizes and binds the analyte and a second portion containing a polynucleotide segment. The polynucleotide segment of the second portion of the bridging entity hybridizes to a signalling entity via a complementary nucleic acid segment in the signalling entity. The signalling entity may be non-radioactively labeled so as to be detectable. The detection of the label indicates the presence of analyte. Kit-like compositions for the practice of the method are also claimed. The specific limitations of certain claims are discussed below as to how they are made obvious by the above combination of

> references. It is noted that the instant claim 283 includes a bridging entity with only one second nucleic acid portion within its scope, but even claims such as instant claim 287 which cites multiple bridging entities lacks limiting these multiple entities as different types or sequences, thus permitting a solution of identical molecules within the scope of claim 287. Also, it is noted that the second part of instant claim 283 gives the signalling part as comprising more than one signalling entity but without requiring either that they must include non-identical entities or that they must contain entities that bind or hybridize to different segments of the second portion of the bridging entity.

On pages 11-12, the Examiner characterized the primary reference (Dunn et al.) thusly:

> Dunn et al. (1977) disclose a sandwich hybridization technique wherein an RNA construct containing two portions performs as a bridging entity as in the instant invention. The two portions of the RNA construct consist of an analyte recognition and binding portion and a tail as discussed on page 23, bridging paragraph between the first and second columns. The tail is a polynucleotide segment that hybridizes to a radiolabelled signalling entity for detection. This detection of the radiolabel is indicative of analyte detection. This methodology is depicted in Dunn et al. (1977) on page 24 in Figure 1 with detection results shown in Figures 2 etc. in the reference. This reference generically discloses the instant invention at said page 23 citation but lacks the use of non-radioactively labeled signalling entity. Additionally, the generic scope of practice of the sandwich hybridization technique of Dunn et al. (1977) is suggested in that the page 23 summary of the technique is generic in nature and the system disclosed by Dunn et al. (1977) to illustrate the technique is stated as being a "model system" on page 23, second column, line 9. These disclosures clearly suggest a scope broader than that of detecting viral RNA map transcription sites as given in the experimental examples in the reference and include detection of other target sites in genomes of organisms such as bacteria etc. It is noted that the radiolabelled signalling entities of Dunn et al. (1977) are prepared via nick translation as is an embodiment of biotin labelling in the below given Ward et al. disclosure.

and on page 12, the secondary reference (Ward et al.) was described thusly:

> Ward et al. generically discloses the substitution of biotinylated nucleic acids as a non-radioactive label for radiolabelled nucleic acids in hybridization detection methods. The disclosure of Ward et al. includes several motivations for the substitution of non-radioactive labels such as based on biotin for radiolabels in columns 1-3 in the section entitled "BACKGROUND OF THE INVENTION" and also gives a reasonable expectation of success for this substitution via numerous examples therein.

leading to his conclusion on pages 12-13:

> Thus, it would have been obvious to someone of ordinary skill in the art at the same time of the instant invention to practice the compositions composed of bridging and signalling entities using non-radioactive labels for detection as instantly claimed because Dunn et al. (1977) disclose a bridging and signalling entities as instantly claimed with radiolabel mediated detection and Ward et al. disclose both the motivation and reasonable expectation of success for substituting non-radioactive labels such as biotin for radiolabel mediated detection during hybridization procedures resulting therefore in the practice of the instantly claimed invention. It is noted that the labelled signal entities of Dunn et al. are disclosed as a nick translated preparation of molecules but that this is not outside of the scope of the instantly rejected claims as noted above. The nick translated signalling entities are a heterogeneous mixture of various different fragments produced by the nick translation processing. These fragments hybridize to different segments of the bridging entity within the target sequence thereon due to their heterogeneous fragment nature but yet directed to said target. Since the nick translation process is variable regarding the number of nucleic acid fragments made thereby the process reasonably results in many different ratios regarding hybridized segments in the bridging entity as well as how many signalling entities there are relative to the bridging entities thus suggesting a wide range of ratios as given in a number of the instant claims between different parts of the instant invention. Instant claims such as claim 334 are included as rejected hereinunder due to the above noted unclarity regarding the word "derived".
>
> The obviousness rejection is respectfully traversed.

As in the case of the previous anticipation rejection, the instant obviousness rejection is predicated on a basic misunderstanding and mischaracterization of Dunn's disclosure. Applicants respectfully disagree with the assertion that Dunn et al. "generically discloses the instant invention at said page 23 citation but lacks the use of a non-radioactively labeled signalling entity." As elaborated hereinabove, Dunn's is a sandwich hybridization in which the analyte adenovirus RNA is sandwiched between two probes, one being Adenovirus 2 DNA immobilized on a nitrocellulose filter, and the other being SV40 ^{32}P-labeled DNA. In Dunn's disclosure, the two probes in the sandwich clearly bind to different sequences on the target adenovirus RNA analyte, unlike the instantly claimed invention in which the signalling entity binds or hybridizes to a molecular bridging entity, and the latter binds or hybridizes to an analyte having a molecularly recognizable portion thereon. Moreover, the instant invention requires that the signalling entity be substantially incapable of binding to or hybridizing with the analyte molecularly recognizable portion. Because theirs is a sandwich hybridization in which the target RNA analyte is sandwiched between the immobilized DNA probe and the radiolabelled SV40

DNA fragment, Dunn et al. teaches away from the instant invention.

Clearly, there is a total lack of identity, teaching or even a suggestion in Dunn et al. with respect to the recited signalling and molecular bridging entities as set forth in the instant claims. As indicated in the previous art rejection under §102, the instant invention can be distinguished on at least three or four material elements from Dunn's disclosure:

- the molecular bridging entity and the signalling entity are capable of binding to or hybridizing with each other through their respective nucleic acid portions

  (contrast with Dunn et al. whose two probes hybridize to different portions of the target RNA analyte)

- the signalling entity is substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte

  (contrast with Dunn et al. where the 32P-labeled SV40 DNA probe hybridizes to the target RNA analyte)

- the complementary sequences corresponding to the molecular bridging entity and the signalling entity can never lie in one continuous chain because the signalling entity is substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte

  (contrast with Dunn et al. who "demonstrated the existence of an RNA molecule consisting of Ad2 and SV40 sequences in <u>one continuous chain</u>.")

- the present invention provides a universal concept and system applicable to universal array of analytes and where the signalling entities can be universally used regardless of molecularly recognizable analyte portions

  (contrast with Dunn et al. who used DNA probes for detecting RNA transcript analytes)

The assertion that Dunn's disclosure is somehow a "model system," suggesting a scope broader than that of detecting viral RNA map transcription sites as given in their experimental examples flies full face not only against not their cited 1977 <u>Cell</u> paper, but Dunn's subsequent 1978 <u>Cell</u> paper and 1980 <u>Methods in Enzymology</u> article, as well as the entire scientific and patent literature. As

indicated in the anticipation rejection discussed *supra*, author Dunn had plenty of time and opportunity to clarify the "model" aspects of his 1977 work. The clear fact remains: neither the cited authors nor did anyone else in the scientific or patent literature seize upon Dunn's 1977 Cell disclosure as a "model system" beyond mapping viral RNA transcripts using sandwich hybridization and a DNA probe immobilized on a nitrocellulose filter. And the reason why others and the authors themselves could not extrapolate upon the cited 1977 Cell paper was quite simple: Dunn's 1977 disclosure was not a model system that would have led the ordinarily skilled artisan to Applicants' invention. Dunn's own words are dispositive on the issue:

> We have developed a technique (sandwich hybridization) in which RNA is hybridized to defined fragments of viral DNA bound to nitrocellulose filters such that the 3' or 5' end of the RNA protrudes as a single-stranded tail. The DNA sequences complementary to the "tail" sequences can be determined by a second round of hybridization using specific fragments of viral DNA labeled with ^{32}P. **By using DNA radioactively labeled to high specific activity in vitro as a probe, we have overcome some of the limitations to mapping RNA labeled in vivo**.
>
> As a model system, we have used RNA from cells productively infected with an Ad2-SV40 hybrid virus, Ad2+ND1, originally isolated by Lewis et al. (1969). Ad2+ND1 contains a 0.94 kilobase (kb) insertion of SV40 DNA which replaces 1.9 kb of the Ad2 genome located between positions 80.6 and 86 on the conventional physical map of Ad2 . . .
>
> [Dunn et al., Cell (1977), page 23, last paragraph, bottom left column, through first full paragraph, right column]

Two years after Dunn's first 1977 Cell paper on sandwich hybridization, there followed two other Cell papers, one by Kimmel and Firtel ["A Family of Short, Interspersed Repeat Sequences at the 5' End of a Set of Dictyostelium Single-Copy mRNAs," Cell 16:787-796 (April 1979)] and the other by Long and Dawid ["Expression of Ribosomal DNA Insertions in Drosophila melanogaster," Cell 18:1185-1196 (December 1979)]. A copy of the aforementioned Kimmel and Firtel (1979) and Long and Dawid (1979) are attached hereto as Exhibits 42 and 43, respectively. In both instances, Dunn and Hassell's sandwich hybridization was repeated to the letter for RNA mapping studies and analysis.

In studying the RNA transcripts in slime mold (Dictyostelium), Kimmel and Firtel disclose on page 792 of their paper:

> **Bands 3 and 4 Are Part of a Single Transcription Unit**
> The data presented in the previous sections suggest that a large

fraction of the different members of the M4 repeat family and adjacent single-copy sequences are transcribed into mRNA. To determine whether the RNA transcripts complementary to bands 1-3 represent one of these single-copy transcripts, sandwich hybridization experiments were carried out using the method of ***Dunn and Hassell (1977)***. DNA of subclones 1, 2 and 3 was digested with Pst I to excise the Dictyostelium insert. The digests were then electrophoresed on agarose gels and transferred to nitrocellulose filters by the method of Southern (1975). The DNA blot filter was then hybridized with unlabeled poly(A)+ RNA (see Figure 7A). If an RNA complementary to band 1-3 contained the repeat sequence found in band 4, it should also be a site for hybridization of a band 4 probe. It can be seen in Figure 7 that the RNA which hybridizes to band 3 will hybridize to nick-translated band 4. Some nonspecific binding of ^{32}P band 4 to the pBR322 vehicle is observed, as is binding to bands 1 and 2. This background, however, is considerably less than the specific hybridization of band 4, which is dependent upon the presence of the low abundance class (0.01% of total mRNA) band 3 mRNA. We conclude that band 4 is not part of the 0.9 kb mRNA transcription unit and that the 0.9 kb mRNA complementary to both fragments 1 and 2 does not contain this repeat sequence.

Control experiments in which band 3 RNA hybrids were treated with a low level of ribonuclease prior to the addition of band 4 show that the hybridization of the band 4 probe requires an RNA tail sensitive to RNAase treatment (data not shown). When similar sandwich hybridizations are performed using separated strands of band 4, only the upper strand hybridizes to band 3 complementary RNA (see Figure 7). This result is consistent with the data described previously, indicating the asymmetric transcription of the repeat, and further defines the specificity of the sandwich hybridization. From these data, we conclude that fragments 4 and 3 comprise a single transcription unit.

[Kimmel and Firtel (1979), page 792, Exhibit 42; emphasis added]

The above procedure was also repeated in the "Experimental Procedures" section at the end of their paper (see Kimmel and Firtel (1979), page 795, right column under "Hybridizations").

Similarly, Long and Dawid (1979) were pursuing RNA transcript mapping, this time in mosquitos (Drosophila):

Identification of RNA Molecules Containing Ribosomal and Insertion Sequences

We have so far established that, although rare, insertion transcripts exist in D. melanogaster embryos. Some sequences homologous to ribosomal insertions exist outside the rDNA locus in the genome of D. melanogaster (Dawid and Botchan, 1977), it remains to be established what sequences flank the insertions in those transcripts. We tested whether insertion transcripts were derived form ribosomal DNA by "sandwich-hybridization," a method first described by **Dunn and Hassell (1977)**.

In the first series of experiments, we transferred restriction

> fragments of insertion DNA onto nitrocellulose filters. These filters were hybridized with unlabeled nuclear or cytoplasmic RNA and washed extensively to remove unhybridized RNA. They were then hybridized again with ^{32}P-labeled DNA fragments derived from the ribosomal gene. These DNA probes did not share any homology with insertion DNA fragments on the filter because they were derived from a continuous repeat of cloned rDNA. Hybridization could therefore only occur with tails of RNA molecules that had hybridized to an insertion fragment during the first round of hybridization. The results showed that rRNA molecules which contain insertion sequences exist (Figure 6). . .
>
> [Long and Dawid, page 1188, Exhibit 43; emphasis added]

The authors repeated the above description in the "Experimental Procedures" section of their paper (see page 1195 under "Hybridizations")

And in the patent literature, one need only look to Ranki's U.S. Patent No. 4,486,539 for an insight into how the patent world viewed Dunn's so-called "model system." In arguing for novelty and nonobviousness against Dunn's cited disclosure, Ranki et al. argued that a one step hybridization was faster and cheaper than Dunn's two step hybridization:

> The one-step sandwich hybridization method is essentially an improvement over the two-step sandwich hybridization method introduced by Dunn et al. in 1977. . . The sandwich hybridization test described by Dunn et al (1977) and others is a true two-step hybridization test necessitating two separate hybridization steps. A first hybridization step occurs between the DNA on the solid support and the sample nucleic acid. This first hybridization step is followed by extensive washing and a second hybridization step involving a radioactive probe. In the one-step sandwich hybridization test, the two hybridizations are performed simultaneously in a single step without any interrupting washing step. One-step sandwich hybridization requires only half of the time required by two-step sandwich hybridization. In addition, the amounts of washing mixtures and hybridization mixtures are lessened, thereby lowering the cost of the test.
>
> [Ranki et al., U.S. Patent No. 4,486,539, December 1, 1983 Amendment, page 9]

As noted so often in the past in predecessor applications, Ranki's patent disclosure clearly teaches away from the instant invention because it requires a sandwich hybridization in which two probes hybridize to different portions or sequences in the target analyte polynucleotide. In the invention at hand, the signalling entity binds to or hybridizes with the molecular bridging entity second portion through the nucleic acid portion - not to the analyte as is required in sandwich hybridization practiced by Dunn's or Ranki's groups.

To recap the series of historical events commencing with the cited Dunn and Hassell (1977) Cell paper and leading up to the present invention, the scientific community extended the former's work on RNA transcript mapping in virus-infected CV-1 cells (a line of African green monkey kidney cells) to RNA transcript mapping in slime mold (Kimmel and Firtel (1979)) and mosquitos (Long and Dawid (1979)), and the patent community reduced the number of hybridization steps in Dunn's disclosure from two to one (Ranki et al., U.S. Patent No. 4,486,539). Such developments do nothing to establish Dunn's disclosure as a "model system." If anything, the intervening publications and patent applications between Dunn's 1977 Cell paper and the May 5, 1983 first filing of Applicants' patent application establish the nonobviousness of the present invention because all continue the sandwich hybridization technique first disclosed in Dunn et al. (1977).

Sandwich hybridization teaches away from the present invention, as discussed *supra* (see this Amendment, page 62, first and second full paragraphs *et. seq.* for discussion in connection with the anticipation rejection (§102(b)) of the material differences between sandwich hybridization and the presently claimed invention). The former relies on two probes that hybridize to different sequences in the analyte. Moreover, as disclosed in Dunn et al. (1977), the RNA analyte molecule was demonstrated to consist of sequences corresponding to the two DNA probes which were in one continuous chain. In sharp contrast to sandwich hybridization and Dunn's disclosure, the present invention only requires that one element - the molecular bridging entity bind to or hybridize with an analyte. The other element, the signalling entity, is substantially incapable of binding to or hybridizing with the molecularly recognizable portion on the analyte. Moreover, the analyte in the present invention could never have in one continuous chain the sequences corresponding to the complementary sequences in the molecular bridging and signalling entity. The reason: the signalling entity never binds to or hybridizes with the analyte or the analyte molecularly recognizable portion.

Because Dunn et al. and their sandwich hybridization technique did not disclose or suggest the instant invention for reasons discussed *supra*, the addition of Ward's pioneering U.S. Patent No. 4,711,955 as a secondary document does not bolster the rejection to render the instant invention obvious. Substituting Ward's non-radioactive labels for Dunn's radioactive ^{32}P-labels does not reach the present invention and its signalling and molecular bridging elements as defined in the instant claims. Dunn's disclosure would still require the ordinarily skilled artisan

to use the sandwich hybridization assay in which two nucleic acid probes hybridize to different portions of a target polynucleotide analyte, the latter having complementary sequences to the two probes lying in one continuous chain.

Nor should it in any be overlooked that any modification to Dunn's disclosure in order to reach the present invention must necessarily entail the destruction of the intended purpose or function of the sandwich hybridization technique. The Federal Circuit has definitively held such modifications as being nonobvious. In the case, In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), the Court provided the following analysis:

> We are persuaded that the board erred in its conclusion of prima facie obviousness. The question is not whether a patentable distinction is created by viewing a prior art apparatus from one direction and a claimed apparatus from another, but, rather, **whether it would have been obvious from a fair reading of the prior art reference as a whole to turn the prior art apparatus upside down**. French teaches a liquid strainer which relies, at least in part, upon the assistance of gravity to separate undesired dirt and water from gasoline and other light oils. Therefore, it is not seen that French would have provided any motivation to one of ordinary skill in the art to employ the French apparatus in an upside down orientation. The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. [citations omitted] [221 USPQ at 1127; bold added]

The Court's punchline followed in the next paragraph of its Opinion:

> Indeed, **if the French apparatus were turned upside down, it would be rendered inoperable for its intended purpose**. The gasoline to be filtered would be trapped in pocket 9, and the water French seeks to separate would flow freely out of the outlet 5. Further, unwanted dirt would build up in the space between the wall of shell 1 and screen 21, so that, in time, screen 21 would become clogged unless a drain valve, such as pet-cock 13, were re-introduced at the new "bottom" of the apparatus. [citations omitted]
>
> [*ibid.*, page 1127; bold added]

Having the cited Dunn and Ward documents in hand, the skilled artisan would have had to modify the former's disclosure by changing the sandwich hybridization technique in at least two major and significant respects. First, such a person would have had to destroy any analyte recognition capability in the signalling probe. This would have meant rendering the ^{32}P-labeled SV40 DNA incapable of hybridizing to the adenovirus RNA analyte. Second, the skilled person would have also had to modify both Dunn's immobilized Ad2 DNA and the ^{32}P-

labeled SV40 DNA so that they would hybridize to each other. In short, this would have entailed adding complementary nucleic acid portions respectively to Dunn's two probes. But the reader of Dunn's disclosure would have been discouraged to try such purpose or function destroying modifications because Dunn et al. go to great - almost incredible - lengths to extoll the virtues of their sandwich hybridization technique:

> The **high sensitivity of this technique** [sandwich hybridization], achieved through the use of 32P-labeled RNA of high specific activity, has led to the observation . . .
> [Dunn et al., Cell 12:23 (1977), Sumary; bold & parenthetical added]

> By **using DNA radioactively labeled to high specific activity in vitro as a probe** [to the analyte], we have overcome some of the limitations to mapping RNA labeled in vivo.
> [*ibid.*, page 23, right column, first paragraph; bold & parenthetical added]]

> Moreover, the **high level of sensitivity afforded by the sandwich hybridization technique** has led to the unexpected observation . . .
> [*ibid.*, page 24, left column, first paragraph; bold added]

> The **high sensitivity of the technique** [sandwich hybridization], achieved through the use of radioactive DNA of very high specific activity, should allow mapping of minor RNA species and of RNAs having homology with only a limited area of the genome . . .
> [*ibid.*, page 31, left column, first paragraph under **Discussion**; bold & parenthetical added]

> The **sensitivity of the sandwich hybridization technique** has enabled us to detect homology between the Ad2 + ND1 hybrid RNA and several areas of the viral genome distal to the SV40 insertion.
> [*ibid.*, page 31, right column, full paragraph; bold added]

Neither of the cited documents - Dunn et al. or Ward et al. - would have provided the reasonable expectation of success to modify the sandwich hybridization technique to the point of total disruption and destruction. Certainly, after numerous passages lauding the sandwich hybridization technique for its high sensitivity and advantages, the authors themselves, Dunn and Hassell, would have scoffed at the idea of modifying it. And Ward who discloses analyte-specific non-radioactively labeled nucleic acid probes, would have provided likewise no motivation to even try such modifications to Dunn's sandwich hybridization technique.

Equally telling are the historical events the followed Applicants' seminal May

5, 1983 filing date. Within a year and a half later, the predecessor assignee had already disclosed the invention through product development releases, at one and maybe more professional conferences including posters and at least one abstract, dissemination of product literature, actual sales of its Bio-Bridge® product, and the publication of its corresponding European patent application on December 19, 1984. It is clear and indisputable that at least in 1984 Applicants publicly disclosed their invention in at least one and maybe more professional conferences. At the 75th Annual Meeting of the American Society of Biological Chemists held June 3-7, 1984 in St. Louis, Missouri, the predecessor assignee presented a series of posters and an abstract disclosing one embodiment of Applicants' invention. A copy of the abstract titled "Non Radioactive Biotin - Dependent Hybridization/Detection Using Unlabeled Probe DNA," coauthored by among others, Dr. Engelhardt, is attached as Exhibit 44. This abstract (Exhibit 44) was published in Federation of American Societies for Experimental Biology (FASEB) 43:2048 (May 4, 1984), as Abstract No. 3671. A copy of the posters that were presented at aforementioned June 1984 meeting are also attached as Exhibit 45. Even more significant are the predecessor assignee's sales of its Bio-Bridge™ Labelling System and Bio-Bridge™ Labelling Molecule. A copy of a product brochure disseminated to the public in November 1984 listing both aforementioned products is attached as Exhibit 46. In the product brochure (Exhibit 46), reference is made to the notation at the bottom of page titled "ORDERING INFORMATION." The notation "8411" refers to the eleventh month of 1984, or November 1984.

No less than two significant companies and a major university filed patent applications and obtained U.S. patents for subject matter embraced by Applicants' universal invention. These developments are described in the opening remarks of this Amendment (see this Amendment, page 29, last paragraph, through page 31, first full paragraph) and include, of course:

> Amersham's U.S. Patent No. 7,716,106 (Chiswell) [Exhibit 1];
> Chiron's U.S. Patent No. 4,868,105 (Urdea et al.) [Exhibit 2]; and
> Princeton's U.S. Patent No. 4,882,269 (Schneider et al.) [Exhibit 3].

At the risk of some redundancy, the following events took place after Applicants' May 5, 1983 priority filing date and public disclosure of their invention and the disclosure and/or sale of the instant Assignee's BioBridge™ product.

On February 28, 1985, Amersham International plc of England filed U.S. Patent Application Serial No. 706,747, for "Detecting Polynucleotide Sequences" based on a priority United Kingdom application 8405437 filed on March 1, 1984. In that patent application, the inventors claimed:

> 1. A method of detecting a specific target polynucleotide sequence in a sample, comprising the use of
>
> a) a labelled polynucleotide secondary probe having a complex single-stranded polynucleotide sequence, and
>
> b) a polynucleotide primary probe having a single-stranded sequence complementary to the target sequence and a complex single-stranded sequence complementary to the complex sequence of the secondary probe,
>
> which method comprises the steps of
>
> i) contacting the sample under hybridisation conditions with the primary probe,
>
> ii) before, during or after said contact hybridising the labelled secondary probe to the primary probe, and
>
> iii) observing the presence or absence of the label in association with the sample as indicating the presence or absence of the target sequence.

Amersham's '747 patent application eventually issued on December 29, 1987 as U.S. Patent No. 4,716,106 [copy attached as Exhibit 1].

On December 11, 1985, Chiron Corporation filed U.S. Patent Application Serial No. 06/807,624 for "Solution Phase Nucleic Acid Sandwich Assay." In an amendment filed in that patent application shortly after the issuance of the first office action, the inventors claimed:

> An assay method for detecting a nucleic acid sequence in a sample, employing two sets of reagents: a labelling set; and a second capturing set, said method comprising:
>
> combining in a liquid medium under binding conditions for complementary pairs, said sample containing analyte in single-stranded form, members of said labelling set of reagents comprising:
>
> (a) one or a plurality of labelling nucleic acid probes comprising polynucleotide chains each having two nucleic acid regions, the first region having a nucleic acid sequence L-1 at least about 15 nucleotides in length which is complementary to a sequence of said analyte, and the second region having a labelling reagent recognition sequence L-2, wherein when said labelling set includes a plurality of nucleic acid reagents, each of said sequences L-1 is complementary to physically distinct, nonoverlapping sequences of said analyte; and
>
> (b) a labelling reagent having a nucleic acid sequence complementary to said labelling reagent recognition sequence L-2 and a label which provides,

directly or indirectly, a detectable signal; and

members of said capturing set of reagents comprising:

(c) one or a plurality of capturing nucleic acid probes comprising polynucleotide chains each having two polynucleotide sequence regions, the first region having a nucleic acid sequence C-1 which is complementary to a sequence of said analyte, and the second region having a capturing reagent recognition sequence C-2, wherein said sequences L-1 and C-1 are nonidentical, noncomplementary sequences that are each complementary to physically distinct sequences of said analyte, and wherein when said capturing set includes a plurality of capturing nucleic acid probes, each of said sequences C-1 is complementary to physically distinct, nonoverlapping sequences of said analyte; and

(d) a capturing reagent having a nucleic acid sequence complementary to said capturing reagent recognition sequence and capable of binding, directly or indirectly, to a solid support;

separating said label into a bound phase and an unbound phase by means of said solid support; and

detecting the amount of bound or unbound label as determinative of the presence of said analyte.

Chiron's '624 patent application eventually issued on September 19, 1989 as U.S. Patent No. 4,868,105 [copy attached as Exhibit 2].

Curiously two days after Chiron's filing, Princeton University filed U.S. Patent Application Serial No. 808,695 for "Amplified Hybridization Assay" In that patent application filed on December 13, 1985, the inventors claimed:

1. A method for the detection of a target nucleotide sequence, comprising:

a) contacting the target nucleotide under conditions that permit hybridization with (i) a primary probe which comprises a polynucleotide sequence that is complementary to the target nucleotide sequence and a polymeric tail that has binding sites that are incapable of binding to the target sequence, and (ii) a plurality of secondary probes comprising a family of signal-generating probes each member of which comprises a polymer capable of binding to a portion of the tail of the primary probe and a signal generating component; and

b) detecting the signal generated by a reaction product formed in step (a).

Princeton's '695 patent application eventually issued on November 21, 1989 as U.S. Patent No. 4,882,269 [copy attached as Exhibit 3]. This patent was licensed to Imclone, Inc. of New York City who later licensed it to Abbott Laboratories, Inc.

On top of those applications and already issued U.S. patents, Applicants can

point to at least two major lines of diagnostic products that fall within their invention. The first is Chiron's branched DNA product, also called "bDNA." A copy of selected pages from Chiron's bDNA promotional literature is attached as Exhibit 47. The second is Imclone's "Ampliprobe" product line that is also referred to as the "Christmas tree.". A copy of Ampliprobe's literature is attached as Exhibit 48.

With respect to Amersham's U.S. Patent No. 4,716,106 (Exhibit 1) and Princeton's U.S. Patent No. 4,882,269 (Exhibit 3), two different Dunn publications were cited as a basis for rejecting the claims in then-pending patent applications. In the case of Amersham's '106 Patent (then-pending U.S. Patent Application Serial No. 706,747), claims 4-7 and 9-10 were rejected under 35 U.S.C. §103 as being unpatentable over Dunn et al. [Methods in Enzymology 65:468-478 (1980)]. In responding to that rejection, Amersham wrote on June 5, 1987:

> The system described by Dunn et al. is not designed for the same application as Applicant's system. Dunn et al. is detecting RNA between two separate and unique probes - "the target is the meat in the sandwich". Several passages in the publication confirm this, e.g. page 468 paragraph 2 line 2 ".....analyze the transcription products" i.e. the RNA; page 476 paragraph 3 "This approach seems particularly valuable for detecting and mapping viral transcripts".
>
> Dunn et al. does not teach the commercially valuable concept of a universal labelled probe which is central to Applicant's invention. Both the probes in the Dunn et al. system are specific to each individual target.
>
> In the Dunn et al. system the two probes are brought together by the target. In Applicant's invention, the two probes hybridize independently of the target and only one of the probes hybridizes to the target. Claim 1 limits the subject invention specifically to probes that anneal to each other.
>
> There is a fundamental problem with the approach of Dunn et al. Hybridization reactions are driven by the reactant in excess. The effective concentration in the hybridization solution of the probe bound to the filter is low (i.e. although the local concentration on a band is high the effective concentration in the liquid phase is low); therefore, the reaction between it and the target is driven by the concentration of the target. As the target concentration is generally low, the inherent inefficiency of this approach results in a loss of sensitivity, severely limiting its applicability. To the best of Applicant's knowledge, the Dunn et al. technique has never gained acceptance.
>
> [U.S. Patent Application Serial No. 706,747,
> June 5, 1987 Amendment, page 4,last paragraph,
> through page 5, third paragraph]

Amersham's remarks convinced the examiner who wrote in an August 20, 1987 Examiner Interview Summary Record:

> Indicated that the claims were in condition for allowance, but required the amended addition of the word --sequence-- following "target" in claim 1, line 7 for proper antecedent basis. Indicated the above conection(sic) would be made by Examiner's Amendment.
>
> [U.S. Patent Application Serial No. 706,747; August 20, 1987 Examiner Interview Summary Record]

In its '269 Patent, Princeton University argued against an obviousness rejection over the same Dunn et al. document as Amersham had in its '106 Patent [Methods in Enzymology 65:468-478 (1980)], writing in a February 28, 1989 Amendment:

> The Examiner contends that Dunn teaches the use of universal "tails" in detection in hybridization assays.
>
> This rejection is obviated by the amended claims which positively recite that an amplified signal results from the binding of a plurality of secondary probes to different portions of the primary probe. By contrast to the claimed invention, Dunn does not teach the use of universal "tails" in hybridization and does not teach amplification. As fully explained in the arguments and Declarations submitted by the Applicants in the Parent Application (now abandoned), Dunn does not use universal tails, but rather two very specific probes for the same target - one that hybridizes to and captures the target sequence, and another labeled probe that hybridizes directly to the captured target sequence. In no way does Dunn suggest the amplification achieved by the claimed invention, in which the hybridization of a primary probe to its target is detected using a family of signal-generating secondary probes that bind to different portions of the tail of the primary probe, and not to the target sequence.
>
> [U.S. Patent Application Serial No. 940,712; February 28, 1989 Amendment, page 8, last two paragraphs, through page 9, first paragraph; underline in original]

Princeton's remarks were apparently embraced by the examiner who subsequently allowed the '712 patent application on June 5, 1989, leading to the issuance of the '269 Patent.

As Robert Harmon explained in his chapter on nonobviousness [Patents and the Federal Circuit, 3rd edition, *supra*]:

> (c) Other Objective Indicators
>
> Objective evidence of nonobviousness is not limited to commercial success. Indeed, some of the most potent evidence supporting the patentability of an invention is found outside the marketplace.

> *Copying*. The fact that an accused infringer did not copy any prior art device, but found it necessary to copy the claimed invention is strong evidence of nonobviousness.246 Copying is an indicium of nonobviousness and is to be given proper weight.
>
> [Patents and the Federal Circuit, page 123]

What greater tribute could be paid to the nonobviousness and patentability of the present invention than the indisputable fact that after Applicants' May 5, 1983 seminal filing date and public disclosure of Applicants' invention, three different entities proceeded to file patent application on the same subject matter embraced by the instant claims! And what greater tribute could be paid to the nonobviousness and patentability of the present invention than the incontestable fact that three patents have already been issued from those other three applications!

But an even greater tribute has been paid to the Applicants' invention by the bDNA and Ampliprobe product lines that have been marketed and sold by Chiron and Imclone, respectively. Coupled with the commercial success by others on products covered by the present claims, discussed *infra*, this evidence is both compelling and dispositive on the issue of nonobviousness.

In view of the foregoing remarks and submitted exhibits, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection, thereby placing all of the present claims, 283-362, 364-380, 382-398, 400-404 and 406-460, in condition for allowance. An early indication as to their allowability is respectfully sought.

* * * * * * *

SUMMARY AND CONCLUSIONS

Claims 283-362, 364-380, 382-398, 400-404 and 406-460 are presented for further examination on the merits. Claims 287-294, 300, 310, 313, 319, 322, 343-346, 356, 364-375, 379, 382-393, 397, 400-402, 406-408 and 412 have been amended. In addition, twenty-two new claims (439-460) have been added and four claims (363, 381, 399 and 405) have been cancelled. No new matter has been inserted by any of the foregoing amendments or added claims.

The cost for presenting the twenty-two new independent claims as well as the multiple dependent claims (a total of __ claims) is $____.00. The Patent and Trademark Office is authorized to charge the amount of $____.00 to Deposit Account No. 05-1135. If any other fee or fees are due in connection with this Amendment, authorization is further hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early favorable action on this application is respectfully sought.

Respectfully submitted

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SUMMARY AND CONCLUSIONS

Claims 283-362, 364-380, 382-398, 400-404 and 406-460 are presented for further examination on the merits. Claims 287-294, 300, 310, 313, 319, 322, 343-346, 356, 364-375, 379, 382-393, 397, 400-402, 406-408 and 412 have been amended. In addition, twenty-two new claims (439-460) have been added and four claims (363, 381, 399 and 405) have been cancelled. No new matter has been inserted by any of the foregoing amendments or added claims.

The cost for presenting the twenty-two new independent claims as well as the multiple dependent claims $1,760.00. The Patent and Trademark Office is authorized to charge the amount of $1,760.00 to Deposit Account No. 05-1135. If any other fee or fees are due in connection with this Amendment, the Request for an Extension of Time (2 months), or the accompanying Information Disclosure Statement, authorization is further hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

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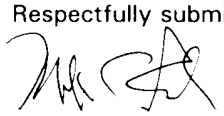
Respectfully submitted



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